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### HORMONES IN RELATION TO REPRODUCTION*

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DEVELOPMENTS have been so enormous and rapid in the field of hormone action in relation to the reproductive system and reproductive phenomena during the last decade that to evaluate its present status is a difficult if not indeed an impossible task. Fluhmann[20] has cited more than two hundred references that appeared within a period of two years, dealing with the phase of ovarian-hypophyseal relationship. Conflicting findings, differences in interpretation, and lack of information will make it evident why some report of progress rather than final solutions will characterize this discussion. Rather than limit the discussion to one or two special problems with which I, personally, may have dealt, it appears more advisable on this occasion to examine the subject on a wider scale and attempt to leave with you a few general principles that appear to exist and that must be taken into consideration in deductive reasoning.

It should be emphasized that reproduction among the different vertebrate classes rests upon a basic plan more or less common to all, and that an understanding of the general problem will be aided by some comprehension of events occurring in organisms other than man. It is well appreciated that minor species differences exist in many of the separate phases, but the notion that events characteristic of other than human forms have no application to man should have been discarded long ago. An attempt will be made, therefore, to outline briefly some of the general phases of reproduction that are associated with hormone

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action, to present several related facts, and to offer some suggestion as to possible ways of interpreting the facts as they apply to the function of reproduction within the organism. Many of the interpretations may well be questioned, and there is no doubt that working hypotheses of the present, even though they prove useful in indicating ways and means of approaching the solution of certain of our problems, will be modified or be totally discarded as new facts and points of view are developed. It will be apparent to all that though great advances have been made in understanding the problems and mechanisms involved in the function of reproduction, a great amount is still awaiting elucidation. The suggestion of a few apparently general principles will be discussed as a basis for offering an interpretation as to the manner in which hormones may operate to control some of the events that characterize the function of reproduction.

1. The first principle to be discussed is the double functional potentiality of the sex glands. These two functions are the maturing of germ cells and production of internal secretions or hormones. It should be properly considered that each of these functions is associated with the phenomenon of reproduction rather than with general bodily health, longevity, mental processes, or religious beliefs. Maturing of germ cells is phylogenetically the older function, hormone secretion the newer.

In the simpler invertebrate forms of life, the germ cell producing function alone appears to characterize the activity of the gonads for we see little or no evidence of hormone action. In the lowest of the vertebrate types there is little hormone action, as compared with the higher types; in some of the lowest vertebrates the germ cells merely escape through the walls of the sex glands and pass to the outside without the use of specialized ducts for carrying them. But as we look at an ascending series of vertebrates, complexities are introduced by the utilization of specialized ducts to transport the sex cells to the outside, or as occurs among some members of every vertebrate group excepting the birds, there is internal insemination and retention of the developing embryo within specialized passages of the parental body. The latter are usually parts of the müllerian duct system in the female.

Characteristic of all reproductive processes is periodicity. Reproduction is not a continously operating process but usually occurs once a year. The accessory structures, as well as the gonads themselves, come into activity only during the reproductive period. The accessory structures make possible the meeting of the germ cells at the proper place, time, and in the proper condition. It is the gonad, therefore, that matures the germ cells and makes certain that the ducts are ready to function at the proper time.

2. The second principle to be emphasized is the control of the essential accessory reproductive organs, the nonessential characteristics, and to

some extent the psychic behavior by the homologous sex hormone and the absence of an effect from the heterologous sex hormone.

The essential accessory reproductive organs include those structures that play an important or necessary rôle in reproduction. In the male these consist of such structures as the entire series of wolffian duct derivatives (epididymis, vas deferens, seminal vesicles) and the prostate and Cowper's glands, penis, etc. In the female it is the müllerian system that operates (the oviducts, uterus, and vagina) and mammary glands. Without emphasizing particularly any rigid classification of nonessential structures, they can be considered to be that miscellaneous set of characters that more or less clearly separate the sexes into dimorphic patterns but which are of no particular functional utility in reproduction as such. The horns of certain male mammals, the nuptial colorations of some lower vertebrates, the comb, wattles and specific feather patterns of birds, the voice and pubic hair distribution in man can be used as examples.

The control of these accessory reproductive organs has been abundantly demonstrated to rest upon the internal secretions of the specific or homologous sex gland. Castration entails the loss of function and involution of the male ducts and glands, which contribute the greatest part of the semen, but their function can be returned by injecting the hormone of the testicle and semen, obviously without spermatozoa, is discharged on mating. The hormonal function, therefore, appears as one of the elements in a more elaborate system than exists in lower forms. The accessory organ function provides a means of transfer of germ cells to the locality that will make possible a meeting with the germ cells of the opposite sex. In lower vertebrates including the mammals the hormones probably play a great part in stimulating the mating reactions, or sex drive, but in primates, especially in man, its rôle in this event is to be questioned to a large extent. Hormone function may be exercised continuously, as in constant breeders like rats, guinea pigs, and human individuals, or periodically as in those forms having a single breeding period during the year. In the latter, however, the period of nonfunction is due merely to the failure of the gonad to secrete its hormone, for injections of potent preparations can stimulate their function at any time of the year.

In the female the control is characteristically a periodic one since the oviducts, uterus, and vagina develop to a high point, recede, and develop again each five days (rat), sixteen days (guinea pig), twenty-eight days (monkey and woman) or once each year (characteristic of wild types). This control involves a preparation again for conducting the germ cells to the proper place whether this be outside the body (perhaps wrapped in protecting substances such as the jelly of amphibian eggs, or the albumin and shell of the hen's egg) or retained within it for development. The latter condition in mammals calls forth still

further specializations such as are involved in implantation, nourishing the embryo through the placenta, and finally delivering it at the proper time. In keeping with these added complexities of control more than one hormone has been elaborated. We know at least two that come from the ovary, estrin which is responsible for the growth changes and to a large extent gland activity, and the hormone of the corpus luteum which plays a large part in uterine responses in a manner that shows clearly a secondary reaction superimposed upon the actions controlled by estrin or the more primitive of the two ovarian hormones (for general references see Allen's *Sex and Internal Secretions*[5]).

An important consideration is the specific rôle played by these substances. The testis hormone, for example, cannot stimulate the müllerian system to its characteristic function; neither estrin nor corpus luteum stimulates the secretory function of the male accessory glands. Estrin and corpus luteum are in a sense cooperating hormones in placental mammals where resides their typical sphere of action.

A final point worthy of mention is that though these gonad hormones are quite sex specific, they are in no sense species specific. Thus testis hormone extracted from bull's testicles will grow combs on castrated cocks, repair castration damages to the accessory reproductive glands of castrated rats or in castrated guinea pigs produce semen that is discharged when proper electric stimulations are employed. Estrin from pig or human follicles serves with ease to control the female reproductive ducts of rats or chickens or induce female feathers in the cock.

3. The third principle to be emphasized is that of the threshold of effectiveness. It is too rarely appreciated that hormone storage does not occur in the body and that the response of an organ depends upon a minimal hormone level for a period sufficient for such a response to occur.

Removal of the ovaries or testicles shows clearly the absence of gonad hormone storage in the body. In female rats the vaginal smear alone shows quickly the absence of estrin and examination of the reproductive tract makes certain of its absence. Injections of estrin into ovariectomized females builds up this tract within approximately forty-eight hours and its immediate decline in the absence of injections is striking. In the male rat removal of the testis is followed by objective cytologic changes in the seminal vesicles within a period of forty-eight hours and in the prostate gland within four days. In the brown leghorn fowl estrin induces a typically colored female feather in the growing follicles but the absence of a single day's injection causes deposition of a pigment band indicative of a sub-effective concentration of the hormone.[29]

The gonad hormones are excreted from the body through the kidneys and the urine is now one of the most common sources for the extraction of these secretions. Whereas there is much yet to learn regarding the

relation of excretion to concentration in the body, or the possible changes in the renal threshold under varying conditions, it is apparent that a great difference exists in the excretion of these materials when injected in aqueous solutions or suspended in oil; they are readily absorbed from the aqueous solutions hence concentrations are more difficult to maintain with aqueous than with oil suspensions.

The threshold of response is an interesting phenomenon for it soon becomes apparent that a given dosage may produce a demonstrable effect upon one organ and not upon another. Thus in the rat it has been maintained that whereas a given dose of estrin will produce a typical cornified vaginal smear and uterine changes it requires many times this amount to induce the typical mating response. Among the tests for the testis hormone in mammals the most sensitive one appears to be the spermatozoon motility test, the least sensitive the electric ejaculation test, with seminal vesicle, prostate and ductus deferens responding to intermediate amounts; the low threshold to the high bears roughly the ratio of 1 to 30.[45, 46, 49] Benoit gives the relative sensitivity of responses to testis grafts in the cock as epididymis and vas deferens the most sensitive and passing upward in response, the comb and wattles, plumage, sexual instinct, with fighting and crowing propensities requiring the greatest amount of hormone for the control. Lillie and his students have shown that feathers on different parts of the body differed in their response to estrin: those on the breast were less sensitive to given dosages than those on the back or tail. Following low dosages, feathers on the back might be entirely female while those on the breast were not affected. This different sensitivity to hormone is correlated with the growth rate of the feathers in the different regions.[29, 30, 37, 38]

It becomes apparent therefore that dosage is an important phase of hormone administration, with gonad hormones as well as with thyroid hormone or insulin. A huge dose weekly does not supplant smaller daily dosages and for satisfactory effects a fairly continuous concentration must be maintained.

4. The fourth principle to receive attention is the lack of effect of gonad hormones upon the gonads themselves. It was once hoped, and still is by many, that the administration of estrin or testis hormone would stimulate the gonads. Close attention to hormone physiology, however, suggests the general principle that no endocrine gland is stimulated by products which it itself produces; the thyroid gland is not stimulated by thyroid powders or thyroxin, the pancreas by insulin, the adrenals by cortin, or the parathyroids by parathormone. There appears to be no logical assumption or demonstrated fact that would suggest that the gonads are stimulated by gonad hormones.

If one examines the observations made on the effects on the intact gonad of administration of gonad hormones those effects are injurious rather than stimulating. Thus injury to the ovary has been reported

after estrin injections into monkeys,[4] dogs,[31] and rats,[36, 42, 43] The general findings are reduced ovarian weights, lack of follicular activity, and atretic follicles; in normal female rats injected with estrin, ovaries have weighed approximately 45 per cent to 50 per cent of those of untreated litter mates. There are numerous reports to the effect that estrin injected into normal males produces injuries to the testes.[17, 34, 48, 77] Prior to 1930 this result was usually attributed to an antagonism existing between the two sexes in the general sense in which Steinach originally applied it, but when it was found that similar types of injuries followed administration of testis hormone to young males,[48] it became evident that another explanation than hormone antagonism was required. Testis hormone injected for periods of twenty days into normal young male rats reduced their testis weight to approximately 50 per cent to 60 per cent of litter mate control testes but stimulated the development of the seminal vesicles to a weight of approximately 400 per cent as compared with untreated controls. The explanation of this finding will appear below.

The general results of injecting gonad hormones into normal animals, therefore, is injury to the gonads (from either sex hormone) and a stimulation of the homologous accessories but not the heterologous ones. Gonads rendered defective by various means such as hypophysectomy or vitamin B deficiency and treated with homologous gonad hormones are not improved by these substances but are aided to recover by treatment with other substances.[41, 50] It appears that the gonad hormones have no stimulating effect upon the gonads themselves but their effects upon homologous accessories are very distinct.

5. The fifth principle to which attention is to be given is the absence in the gonads of the power of self-regulation. They are not autonomous structures endowed with the capacity of deciding when and how they should operate, but we may think of them as operating under the direction of a remote control; the seat of such control is the hypophysis.

Older clinicians had noted the association of atypical conditions in the reproductive tract with disorders in the hypophysis or pituitary gland, and the earlier attempts at hypophyseal ablation further suggested a close association between this system and the small gland attached to the lower surface of the brain. The clear demonstration of such important relationships has now been given abundantly by the striking work of Smith,[69-72] Smith and Engle,[73] Zondek,[81, 82] and Zondek and Aschheim,[83, 84] and by others.

In general it has been shown that successful removal of the pituitary gland entails a severe degeneration of the gonads in either sex. Testes and ovaries become inactive and produce neither germ cells nor internal secretions or hormones, and due to the absence of the hormones the entire reproductive tract undergoes involution essentially as severe as after castration. The introduction of fresh pituitary gland substance im-

mediately after hypophysectomy prevents such a severe inactivation of the entire system, or if the typical changes have been permitted to develop, the fresh gland substance causes the system to be repaired to the normal state structurally and functionally. Furthermore, it was found by Smith and Engle and Zondek and Aschheim that the introduction of fresh pituitary gland substance subcutaneously into very young rats led to a precocious development of the entire reproductive system; this effect is somewhat more pronounced in females than in males. The ovaries increased tremendously in size; many more ovulations occurred in animals before weaning than would ever occur at one time in the normal adult; and the uterine development was quite characteristic of the mature animal.

It has furthermore been shown that substances contained in the urine of pregnant women, likewise, exert a marked stimulating effect upon the ovaries, but in a manner somewhat different from fresh pituitary substance. It is this stimulating reaction that constitutes the basis for the Zondek-Aschheim pregnancy test. Substances that stimulate the gonads have been derived from several sources, such as fresh and dried pituitary material, the placenta, urine or blood of pregnant women, but it is not to be suggested that these materials from different sources are identical. Neither is there conclusive evidence to show that the ultimate source of these materials is the hypophysis. Indeed there are many elements suggesting its origin elsewhere particularly in the decidua or certain types of epithelial growths (chorionepithelioma).

It is to be remembered, therefore, that both functions of the gonad (germ cell production or hormone secretion) depend upon a stimulation from the pituitary gland and that many gradations in gonadal activity can be produced in the amount of stimulating substances present. Zondek has referred to the pituitary as the "motor" for the gonads.

6. The next principle to be emphasized is that hypophyseal activity is modified by the gonad hormones; there is a reciprocal interaction between the gonads and the pituitary. The modification may be expressed as an inhibition, or a suppression, of hypophyseal activity of such a nature that pituitary secretions are delivered into the blood stream in reduced amounts.

The capacity of the pituitary to stimulate the gonads does not remain constant but varies, at least in some forms, in association with the amount of gonadal secretions present in the body. Thus Engle[15] and Evans and Simpson[16] determined that the hypophysis of castrated male or female rats was more potent in its stimulating effect after transplantation into the immature organism than was that taken from normal animals of equivalent age. A similar situation has been demonstrated for the rabbit by Smith, Severinghaus, and Leonard[76] and for the guinea pig by Severinghaus.[67] Thus the presence of a functional gonad is associated with a lowered capacity of the hypophysis to exert its stimu-

lating powers. In ovariectomized women, and some in the menopause, Fluhmann[18, 19] was able to demonstrate the presence of a gonadal-stimulating substance in the blood stream (presumably from the hypophysis) which he was not able to demonstrate in normal women. Hamburger[21] finds gonadal-stimulating substances in the urine of both castrated men and women two months to fifteen years after operation that are different from the pregnancy urine derivatives.

The influence of the gonad hormones in lowering the capacity of the hypophysis to stimulate the gonads has also been demonstrated by injecting normal or gonadectomized animals with these substances, or by causing the intact gonad to secrete a larger amount of hormone than is normal. Meyer, Leonard, Hisaw and Martin[36, 42, 43] injected normal female rats with estrin and determined that their hypophyses were decidedly less effective as stimulating agents than those removed from untreated litter mate females. Furthermore, castrate hypophyses though ordinarily possessing greater stimulating power than normal ones do not show more activating powers if the castrate animal has been treated with estrin. Instead of injecting the gonad hormones so as to increase their concentration in the animal body, one can cause the intact gonad to secrete greater quantities if the animal is treated with gonadal-stimulating agents, such as prolan (a urine derivative). Thus the hypophyses of such animals are subjected to the effects of greater than normal concentrations of gonad hormones. Kuschinsky[33] and Leonard[35] have found that hypophyses from normal male and female rats treated with prolan are less effective than those from untreated animals. That this lowered capacity is due to the excess gonad hormone arising from the stimulating action of prolan on the gonad and not from the action of prolan on the hypophysis is indicated by the fact that injections of prolan into the gonadless animal does not reduce the stimulating capacity of the pituitary when this is compared with castrates not so treated.

In still another manner the variation of the stimulating capacity of the pituitary associated with gonad-hormone concentrations is indicated. Smith and Engle[74] found the hypophysis of female guinea pigs at estrum to have less gonadal-stimulating capacity than those during diestrus. Estrum marks the climax of the estrus cycle and is the end of a period in which the female hormones have been present in amounts sufficient to bring on the changes characteristically associated with mating. A low activity of the hypophysis at this time gives some basis for assuming that the depression was brought about by the presence of the gonad hormones whereas in the diestrus phase it is evident that estrin effects are low and probably corpus luteum secretions as well. Excretion or destruction of the gonad hormones therefore can be supposed to release the inhibitory effects on the hypophysis, and it would again come into activity. Wolfe[79, 80] likewise found in the sow a variability

in hypophysis activity during the cycle of the general nature that hypophyses from animals whose ovary contained small follicles up to 6 or 8 mm. in diameter would produce ovulation in rabbits in doses of 1 mg.; hypophyses from animals possessing follicles of 10 mm. diameter required 20 mg.; hypophyses from animals possessing active corpora lutea in the ovaries produced consistent ovulation-inducing stimulation in doses of 40 mg. Thus hypophyses from animals with a progressively increasing gonad hormone content were less and less efficient in their gonadal-stimulating capacity. Freshly developed corpora lutea have been shown by several investigators to contain estrin as well as the corpus luteum hormone. There are many suggestions that corpus luteum hormone, as well as estrin, acts to suppress the hypophysis but to my knowledge the direct evidence has not been presented to show that estrin-free corpus luteum hormone does inhibit the hypophysis. Since the indirect evidence for this is strong it is assumed to be the case for the purposes of this discussion.

If the idea presented above is carried to the state of pregnancy, it should follow that the hypophyses of pregnancy would exhibit a lowered capacity for gonadal stimulation than normal animals. It is during pregnancy that the greatest amounts of gonadal-stimulating substances appear in the urine and to some this has indicated that the hypophysis is more active, not less active. However, since there is no convincing evidence that these substances are actually hypophyseal secretions and since there are many lines of indirect evidence that they are produced not in the hypophysis but in the decidua, more convincing evidence should perhaps be obtained from the effects of transplanting the hypophysis of pregnancy. This has been done in several instances. Bacon[6] found the stimulating power of the hypophysis of pregnancy in the cow to be lower than in the normal animal, and Philipp[60] has found a decidedly less stimulating capacity in the hypophysis from pregnant women. Wolfe[80] used the rabbit ovulating dose of hypophysis and was inclined to believe that the pregnancy hypophysis contained a lower stimulating potency than those from normal animals; his results were not entirely consistent when hypophyses were removed at different stages of pregnancy. Evans and Simpson,[16] however, reported but little difference in the stimulating effect between hypophyses of pregnancy in cows and rats and normal ones.

There appears to be little doubt, therefore, that the gonad hormones do suppress the activity of the hypophysis, and since the evidence indicates that these hormones are without direct effect on the gonads, Moore and Price[48] have interpreted the deleterious effects of gonad hormones on the gonads themselves as being an indirect effect induced by suppression of the hypophyseal secretions that are necessary to maintain the gonads in a functional state. When the gonad hormones which cause gonadal injury are accompanied by some gonadal-stimulat-

ing agent that, temporarily at least, can act for the hypophyseal secretions, then the gonad hormones are not injurious to the gonads.

Since emphasis has been placed upon some of the principles of hormone actions and interactions, it may be of interest to consider some of the possible mechanisms in the actual control of a few of the phenomena characteristic of reproduction. That we do not have sufficient information at the present time to enable us to adequately explain the control of the characteristically rhythmic processes in reproduction cannot be doubted. However, some profit may accrue, at least in suggestions as to ways to consider the various events, in constructing working hypotheses looking to some explanation of the basic phenomena associated with this function.

Certain observations from our laboratory necessitated an explanation along different lines than those current at the time, and a working hypothesis based upon the fundamentals discussed above was attempted. Since many observations from other laboratories appeared also to fit into the conception, it was extended to include a suggested interpretation for other than our own experiments.[44, 47, 48, 51, 55, 68] Stress is laid upon the reciprocal influence between the hypophysis and the gonads as a mechanism for the control of several different events, and I should like to dwell upon this suggested mechanism in considering the control of estrus cycles, of lactation, and of menstruation.

## CONTROL OF BREEDING CYCLES

The breeding cycles of vertebrates, generally speaking, occur once a year, most conspicuous exceptions occurring in birds and mammals, though there are a few special exceptions outside of these two groups. In birds and mammals the majority of species still exhibit the annual cycles, and the spring months are the usual ones for reproductive activity. Among the mammals the yearly cycle is perhaps still the usual one, but the range of cyclic activity is from recurring periods of five days for the rat and mouse, to sixteen days for the guinea pig, and thirty days for the primates, man and monkeys, to the annual period for the wild types. These cycles, ordinarily termed estrus cycles, have as their essential features the increase in size of the uterus, the growth and ripening of follicles in the ovary and the development of a psychic state in the female such that she will mate with a male. The general law of nature, transgressed by the primates, is mating for reproductive purposes only; that is, mating occurs at a point in the cycle best for the meeting of the germ cells.

An attempt has been made to explain the exacting control of these periodic events on the basis of the reciprocal influence between the ovary and hypophysis;[44, 48] at almost the same time and entirely independently a somewhat similar hypothesis was suggested by Brouha and Simonnet.[12] As an example, let us start with a quiescent ovary in the rat. The hypophyseal secretions stimulate the ovary to follic-

ular development and the secretion of estrin. The follicles mature and ovulation occurs. Meanwhile estrin stimulates the reproductive tract and the climax of the cycle occurs with mating. The presence of a high estrin content is necessary to accomplish these changes but as this substance is increased in the organism the hypophysis is so influenced that it delivers an insufficient quantity of its secretions, hence the ovary does not immediately mature a new group of follicles but becomes for a time relatively inactive. When the estrin content is reduced through excretion or possible destruction, the inhibition is removed from the hypophysis, and it again resumes its activity and a new cycle is initiated. The corpus luteum in the rat probably does not play a part in this cyclic control (or if it does a relatively brief one), for it has been demonstrated that the deciduomata reaction of Loeb (a test for corpus luteum hormone) cannot be demonstrated in the rat except by producing a pseudopregnant state; this is accomplished by sterile matings or by mechanical cervical stimulation.[39]

In the somewhat longer cycle of the guinea pig, and that of primates, the corpus luteum probably does play a part. The active corpus luteum phase is longer than in the rat and this fact probably offers an explanation for the longer cycles. Removal of the corpus luteum was long ago shown by Loeb to result in an immediate new cycle and by this means the cycles of the guinea pig can be greatly reduced in length; injections of corpus luteum extracts on the other hand lengthen them.[57] That the long period of ovarian inactivity is due to an insufficient ovarian stimulation, usually provided by the pituitary, is shown by the fact that the ovarian cycle is renewed, even during pregnancy, by the introduction of gonadal-stimulating agents.[58, 80]

The primate cycle has been somewhat modified but is believed to operate similarly. Estrum, or a distinct acceptance period associated with ovulation time, no longer exists but the ovulation cycle is present and the phenomenon of menstruation has been introduced at a midpoint between two ovulation cycles.

A slightly different situation prevails in the estrus cycles of the annual variety. Investigations in this laboratory[51] on the ground squirrel (Citellus tridecemlineatus) found abundantly in the Chicago region show that the ovary is essentially inactive for almost ten months of the year. It can be thrown into activity at any time of the year by the introduction of gonadal stimulants, hence its inactivity is due to an absence of the hypophyseal stimulant. Mr. Simmons has determined that the hypophysis of these forms is inactive during the period of ovarian quiescence but possesses stimulating capacity at the time of the year when ovarian activity is present; stimulating capacity was determined by implantation of the hypophyses into immature female rats.

In these annual breeding types, therefore, hypophyseal inactivity is prolonged instead of temporary as in constant breeding types, and it is recognized that environmental factors play a part in its periodicity. It is assumed that this additional factor from the environment need not be the same for all species. Such environmental agents are not entirely hypothetical, however, and some advancement has been made in acquiring an understanding of them but so far it is only a beginning. Thus Rowan[62, 63] trapped small migratory birds (Junco) on their southward flight from the Alberta region of Canada and confined them in open cages over winter. Lengthening the daily period of light by the use of electric light for ten minutes each day beginning in September and October, in an attempt to duplicate the progressively increasing lengths of spring days, resulted in a stimulation of sexual activity. Despite the external environmental temperatures of from 20 to 40° below zero the testes of these birds increased in weight by hundreds of times and spermatozoa were produced in midwinter. Progressive shortening of the daylight periods led to recessions in this activity and the cycles could be controlled at will. Bissonnette[9, 19] confirmed similar responses to increasing light in the introduced European starling (Sturnus vulgaris).

The stickleback fish (*Gasterosteus aculeatus*) breeds once a year and develops a characteristic nuptial dress during this period. Craig-Bennett, however, was able to induce these changes at will during different seasons in the year by changing the temperature of its habitat. Light manipulations failed to show any influence and the changes were accomplished as well in total darkness by the temperature changes in the light.[14] In one annual breeding mammal (ferret) Bissonnette[11] was able to induce estrus and mating outside of the regular season by progressive increases of the daylight period, and Hill and Parkes[26] obtained evidence that the stimulation in this form operated through the hypophysis. Baker and Ranson[7] modified the breeding of field mice to a marked extent by light.

Thus it is beginning to be recognized that certain environmental agents operate in some manner to influence the hormone activity of the organism; in annual breeding forms this added environmental factor operates upon the controlling mechanism that exists in those forms that are not similarly affected by their environment. In the ground squirrel the environmental factor, or factors, which are operative do not appear to be light. It is not yet entirely clear whether the environmental factor merely operates to stimulate the activity of the hypophysis or operates to remove some analyzable inhibition. The difference may finally prove to be that hypophyses in such annual types do not regain their full activity after the hormonal inhibition is removed, or it may be that a prolonged hormonal inhibition remains until it is released in some manner by the operating environmental agent.

The control of breeding cycles can thus be understood by the application of some of the general principles of hormone action discussed above but that many changes in the hypothesis will be required as our knowledge increases is not to be doubted. The activities of the males can also be understood on the basis of this working hypothesis when the fundamental facts are considered. This has been developed in a paper published elsewhere (Moore[52]).

## CONTROL OF MAMMARY GLANDS

Can this working conception of reciprocal influences of hormones give us any suggestion in regard to the mechanisms operating in the control of growth and function of the mammary glands? It has proved to offer suggestions for experimental work in this laboratory and some of the findings have been interpreted on such a basis. It must be kept in mind that in this phase of reproductive activity there are many species differences but that fundamentally the same concept appears not unreasonable.

Smelser[68] has given a clear demonstration that the mammary glands of castrated male and female guinea pigs respond with equal developmental intensity to the same dosage of estrin injected subcutaneously. The absence of mammary growth in males, therefore, is clearly understandable on the basis of an insufficient amount of estrin to stimulate their development rather than to any inability of these rudimentary structures to respond; equipotentiality of the mammae appears to exist in

the two sexes. A second point is that ovarian grafts in either gonadectomized sex, stimulate mammary growth to a state equal to or greater than that in normal pregnant females, but such hypertrophied mammae do not lactate as long as a functional ovarian graft remains. The peculiarity exists that ovarian grafts in castrated males lead to greater development of the mammary glands than similar grafts in females. Thus in a brother-sister pair of guinea pigs a few days after birth removal of the sex glands of each but with the implantation of one of the ovaries into the male kidney and the other into the female kidney (autograft), the mammary glands of the male always grow larger than those in the female. The explanation of this unexpected result is merely that the ovarian graft in the male secretes a greater amount of estrin due to a greater potency of the male pituitary to stimulate gonadal activity than the female pituitary. This has been shown to hold in another relation by Severinghaus.[67] It is possible that an added factor is introduced in the findings of several investigators that the male hypophysis is less easily modified by gonad hormones than is the female.[28, 54]

Growth and lactation, however, are two different phenomena; since mammary glands induced by estrin injections or by ovarian grafts, or the large mammary glands of pregnancy, do not ordinarily lactate until another stimulus is added.

Stricker and Grüter[78] demonstrated that the injection of pituitary gland substance into rabbits had a lactation-stimulating effect; following a pseudopregnant state the anterior pituitary treatment induced lactation whether the ovaries were present or had been removed. In this laboratory mammary glands were developed in gonadectomized male or female guinea pigs which lactated within forty-eight to sixty hours after pituitary treatment.[55, 56, 68] Riddle, Bates and Dykshorn[61] believe the lactation-stimulating substance of the pituitary is a hormone that differs from the growth or gonadal stimulating hormone. They have named the hormone "prolactin" and it has been reported to have pronounced beneficial effects clinically.[32]

These, and many other findings not mentioned here, emphasize a mechanism in which estrin stimulates the gland to a high state of development and pituitary hormones induce it to lactate. Despite the fact that in the guinea pig lactation can be induced in the male mammary glands under conditions which preclude any effect of the corpus luteum hormone still this in no way proves that corpus luteum fails to play a part even in this species in normal lactation. In some mammals it seems to be well established that the corpus luteum hormone does enter into the chain of events by an effect upon the mammary gland that is superimposed on estrin stimulation. Corpus luteum hormone alone does not influence the mammary growth or secretion. Estrin alone stimulates their growth but in some species this is carried still further by corpus luteum hormone; as long as these hormones predominate, however, lactation does not occur.

Upon the basis of observation and experiment we could suggest the controlling mechanism upon somewhat the same basis as that suggested as operating in the control of the estrus cycles. Thus growth occurs under the influence of estrin and during pregnancy the corpus luteum hormones operate to complete the full development of lobules. At delivery the recession of the corpus luteum and the casting off of the decidua remove the gonad hormones that have suppressed the pituitary gland, and, with the inhibition removed, the pituitary becomes active again and stimulates the mammary gland to lactate. The fact that many animals experience an ovulation immediately after delivery is evidence that the pituitary activity is renewed. The following notations on actual observations of Nelson and Smelser[55, 56, 68] give some

of the bases of fact that suggest this type of control: (1) male or female guinea pig mammary glands stimulated to growth by estrin do not secrete while injections continue. They will lactate, however, (a) if pituitary extracts are administered to stimulate secretion or (b) if estrin injections are discontinued and the animal's own pituitary can come into activity. (2) Ovarian grafts in gonadectomized males or females produce large glands that do not lactate. They will lactate (a) if pituitary substance is given or (b) if the graft is removed and the animal's own pituitary can resume activity. (3) Removal of the ovaries of a pregnant guinea pig may produce abortion but in some cases it does not. If abortion occurs lactation follows; if abortion does not occur lactation does not occur until delivery; after this event all sources of hypophyseal-suppressing gonad hormones are removed (ovary and decidua) and lactation follows. Removal of the ovary and fetus, with retention of decidua, is not followed by lactation but upon removal of the decidua lactation follows. (4) Lactation occurs normally following parturition but it fails to occur if estrin injections are given immediately after delivery. The pituitary that should have become active after delivery was apparently prevented from resuming activity by the injected estrin. Finally, lactation following parturition is prevented by hypophysectomy.[59, 65, 66]

It is to be seen that the reciprocal influence between the ovary and pituitary is suggestive as a means of visualizing a mechanism that may operate in the control of mammary gland activity.

## THE CONTROL OF MENSTRUATION

It may be of interest to carry the speculations still a little farther and inquire whether this working hypothesis holds any suggestions for visualizing the control of menstruation.

The notion has long been current that ovulation and corpus luteum formation were indispensable precursors of uterine bleeding. That notion has now been dispelled as an absolute requirement for external bleeding from the uterus at normal menstruation intervals. The work of Corner[13] and Hartmann,[22, 23, 24] on monkeys presents an abundant amount of evidence that ovulation or the corpus luteum are not required, and Bartlemez[8] has obtained strongly suggestive evidence that a similar condition can be present in the woman.

If we look at the experimental conditions under which uterine bleeding has been induced we find that estrin injection into monkeys leads to growth and development of the uterus, though it does not attain the complete premenstrual stage; it does so, however, if the corpus luteum hormone effect is added to the estrin stimulation.[27] As long as the injection of these hormones continue, bleeding does not occur, but when they cease, bleeding follows.[1, 2, 3, 40, 53] Pituitary substance injected into monkeys with intact ovaries stimulates the ovary to secrete estrin and may cause luteinization but usually external bleeding does not occur as long as the pituitary injections are carried on. When these are stopped, however, external bleeding occurs within a few days.[64] We may see in this the possible recovery of a pituitary to secrete its hormone after the estrin inhibition is removed and acting upon a sensitized uterus, bleeding occurs. Hartman and his colleagues[25] have emphasized more than others the probable rôle of the pituitary in menstrual bleeding and have suggested the possibility of a specific bleeding hormone, but Saiki[64] failed to find it necessary to postulate such a separate hormone. The latter investigator found also that whereas external bleeding was assured after discontinuing pituitary treatment of normal monkeys, bleeding was prevented by the injection of estrin;

when these estrin injections were stopped, bleeding occurred. Smith and Engle[75] similarly induced conditions that were certain of producing bleeding (by gonadal stimulants first, succeeded by ovariectomy), but the bleeding was prevented for periods up to twenty-eight days by injecting corpus luteum extracts having only a trace of estrin. There are many lines of evidence suggesting that the hormone of the corpus luteum exerts a depressing action upon the hypophysis, and it is possible that the control of these experimental types of bleeding will find their explanation upon this reciprocal interrelationship between the gonads and the hypophysis.

Sufficient detail has been presented to indicate that many of the phenomena of reproduction are interpretable upon the basis of the working hypothesis presented. This type of explanation has been of service in this laboratory in suggesting lines of experimental attack upon several problems. It is anticipated, however, that many other factors will be found to enter into the mechanisms of control of the phenomena discussed, and it may be admitted that several facts are difficult to fit into the suggested scheme. With an increase of our knowledge and the evaluation of factual information, there is little doubt that our understanding of the mechanisms of control will advance. It is probable that other endocrine glands will have to be placed in the chain of events as a necessary link, but until the interpretations are clear working hypotheses will have a place.

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## DISCUSSION IN ABSTRACT

PROFESSOR ANDREW CONWAY IVY.—Dr. Moore has made it easier to teach the interrelation between the gonads and the anterior lobe by enumerating the principles of this interrelationship.

In reference to the effect of environmental factors on the functioning of the anterior lobe and gonads, i.e., the effect of light and temperature, it would appear that in these and other instances we have evidence suggesting that the function of the anterior lobe may be affected by factors operating through the nervous system.

I should like to ask whether the atrophy of the testicle which follows the injection of the male sex hormone is due to a direct effect of the male sex hormone on the testicle or to a suppression of the hypophysis by the male sex hormone?

A second question: Is there any recent experimental evidence indicating that the adrenal cortex may be concerned directly with premature development of the gonads? I ask this question, having in mind the fact that adrenal cortical tumors are associated with certain changes attributable only to the gonads. Has anyone shown that the adrenal cortex affects the hypophysis in such a manner as to account for the gonadal changes?

The third question pertains to progestin as related to the paper Dr. Browne has presented. Up until about a year ago there was no direct evidence showing that

progestin is actually formed by the human corpus luteum. I should like to know if there is any recent evidence. That question is intimately related to the clinical use of prolan B or the luteinizing hormone of pregnancy urine, or even of a preparation of progestin made from lower animals.

Before the treatment of essential dysmenorrhea with "hormone preparations" can be placed on a true scientific basis, two types of experiments must be performed in women suffering from essential dysmenorrhea. First, it must be shown by analysis of the blood or urine either that an excessive quantity of estrin is being produced, thus rendering the uterus more irritable, or that there is a retention of estrin in the body due to a decrease in formation of progestin which would also render the uterus more irritable and also according to the work of Smith and Smith, cause retention of estrin in the blood because progestin increases the elimination of estrin in the urine. Second, it must be ascertained if for some reason, either developmental, hormonal or psychic, the musculature of the uterus in the patient is more irritable or sensitive than normal, or the endometrium is abnormal histologically. When such dysfunctions are demonstrated or when the patients are selected on a known etiologic basis and relief from dysmenorrhea is obtained by injection of the hormone indicated for the etiologic condition, then one has adequate reason to state that the relief was not due to psychotherapy but to a true direct response.

Experimental work on animals illuminates the way and provides the indications for what should be tried and expected in the human being.

DR. LEON KROHN.—For several months my associates and I have been treating functional dysmenorrhea with a carefully prepared and standardized preparation of progestin. Our method of approach differs from that of Dr. Browne in that he is attempting to stimulate the production of progestin by using follutein whereas our therapy is substitutional. The experimental work of Novak and Reynolds, Hisaw, Morrell and others suggests the rationale of this procedure.

Dr. Ivy mentioned that in order to justify this form of treatment, one must first demonstrate an abnormally high estrin content in the blood just before the onset of menstruation, in patients suffering with this type of dysmenorrhea. Instead of doing this, we are obtaining a small piece of endometrium a few days prior to the onset of menstruation in an attempt to demonstrate a proliferative type of endometrium instead of the normally present secretory phase. We are also using progestin in the treatment of threatened and habitual abortion.

Although we have not treated a sufficiently large group of cases over a long enough period of time to draw any definite conclusions, the results thus far obtained are very encouraging.

PROFESSOR MOORE (closing).—The contention that gonad hormones are not gonadal stimulants is based upon two lines of evidence: (1) that injection of the gonad hormones in normal animals, or even in cases of experimental gonadal interference, has failed to give evidence of stimulation either from estrin on the ovary or from testis extracts on the testicle. (2) Contrary evidence is available from the fact that actual gonadal injury in both sexes follows injection of gonad hormones into normal animals. The injurious effects noted have been interpreted as indirect effects in which the gonad hormones so act upon the hypophysis as to lower the output of its gonadal-stimulating, or -maintaining, hormone to such an extent there is an insufficient amount of hypophyseal secretions to maintain the gonads in a healthy, active condition. The effect is not believed to be a direct one upon the gonad itself but upon the hypophysis which controls the gonad.

The general scheme of such an interaction as I have indicated for the hypophysis and gonads raises the question of the cooperation of other endocrine products as

mechanisms of control. Time permits the barest suggestion of other conditions that appear to need a new point of view. The notion that exophthalmic goiter is conditioned by a diseased thyroid gland, indicating removal of the organ, may need more mature consideration. Experiments have shown that injections of hypophyseal extracts produce exophthalmos in guinea pigs, either in the presence or absence of its thyroid gland; and that thyroid hyperplasia can be induced by pituitary extract administration. Should we, therefore, question whether the thyroid secretions of a disordered gland are the causative agents or whether the condition of the gland as well as the eye protrusion may not be merely two separate expressions of the same underlying disordered function located elsewhere than in the thyroid gland itself. Sexual precocity may be largely abolished by removal of the sex glands, but these may not be at all the seat of the disorder; they are merely responding to a disordered function located elsewhere. Sufficient knowledge of the biology underlying them may perhaps change radically the present methods of approach in treatment.

We cannot yet, I think, adequately place the adrenals in their possible cooperative position in regard to reproduction. Such findings as precocious sexual maturity associated with hypernephromas and the normal restoration upon removal of the tumor give us the available evidence of interrelationships. One group of workers affirms, and another denies, that cortical hormone administration induces precocious sexual maturity.

The pineal influence is equally intangible. Some pineal tumors have been associated with certain sexual disorders but another similar tumor may not be so associated. Experiments on pineal implants have been disappointing in offering suggestions as to its effect.

I believe Dr. Ivy's remarks regarding the rôle of corpus luteum hormone in quieting uterine motility as an explanation of effects in cases of dysmenorrhea are well taken. The work of Reynolds and Novak makes it appear probable that they are working along correct lines.

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**Halbrecht, B.: Recurrence of Fetal Malformations,** Bull. de la Soc. d'obst et de gynéc., p. 99, January, 1934.

The author reports two cases where fetal monsters were born twice to the same mother. In the first case, both babies had hydrocephalus. The second patient first gave birth to a hydrocephalic child and in a subsequent pregnancy she bore an anencephalic monster.

In both cases the Wassermann reaction was negative. In the other cases of fetal monsters which the author has seen during the past ten years the incidence of positive Wassermann reactions was no greater than among the rest of the obstetric patients. This is not astonishing according to the author because we cannot rely upon the Wassermann test in cases of hereditary syphilis. He believes that fetal malformations most likely represent hereditary syphilis in the second and third generation. Noteworthy is the fact that at autopsy there is no evidence of syphilis. In spite of this, the author believes that such cases should be treated specifically for syphilis.

J. P. GREENHILL.

# THE FETAL MORTALITY IN DIFFERENT TYPES OF TOXEMIA*

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*(From the Sloane Hospital for Women)*

THIS study is a review of 1,500 cases from the records of the Sloane Hospital for Women. Only 1,156 cases are reported, however, for some were deemed either not toxic, or the work-up in the earlier cases was insufficient to establish a definite diagnosis. The study includes the cases since the unit system went into effect in 1922. All the charts signed out as *toxemia* were used; cases of pernicious vomiting were omitted.

Among the 1,156 cases, 120 patients had pregnancy terminated early, either by dilatation and curettage or by hysterotomy. There are, therefore, 1,036 cases which are included in the principal portion of the paper.

For an analysis of this type to be of value, it is essential to have definite clinical criteria for the classification of the cases. Every author, medical school, and hospital has its own classification of toxemia. These classifications are as varied as the theories of the etiology of the convulsive state associated with pregnancy. Time alone will reveal which may be correct. The name of an illness should be such that the trained physician will immediately associate it with a definite symptom group and a definite clinical course. This should not be variable and should be the same regardless of location or school.

For this reason each type of toxemia whose fetal prognosis is under discussion is described, and each case is pigeon-holed according to symptoms, laboratory findings, and clinical course, and *not* according to terminology. Regardless of classification, these cases may be recognized everywhere and a statistical prognosis made.

## HYPERTENSIVE GROUPS

Because hypertension is its outstanding feature, the largest group of the series, 585 (56.5 per cent) is named the hypertensive group and it is divided into three subdivisions: mild, moderate, and severe.

*Mild Hypertension.*—The mild cases that fall into this group have systolic blood pressure readings of 130 to 150, and diastolic readings of 90 to 110. There cases may present no disturbance other than an elevated blood pressure. The elevation may begin at any time during pregnancy but generally in the later months. It may be present for two, three, or more determinations. Postpartum it returns to normal.

*Read at a meeting of the New York Obstetrical Society, May 8, 1934.

In future pregnancies it is likely to reappear but this is not absolute. If it should then be present, it may be of the same level or, more frequently, it is a little higher. These patients feel perfectly well and have no complaints. Occasionally they may develop slight edema of ankles or hands or of both. The urine examination is negative, although occasionally a very faint trace of albumin may be found. The blood chemistry and renal function tests are normal. The eyegrounds may be normal or there may be the early vessel changes of spasticity.

TABLE I. THE FETAL MORTALITY IN PREGNANCY TOXEMIA

| TYPE OF TOXEMIA | NUMBER OF CASES | FETAL DEATHS DUE TO TOXEMIA | MORTALITY PERCENTAGE |
|---|---|---|---|
| Hypertension | | | |
| Mild | 338 | 11 | 3.0 |
| Moderate | 197 | 7 | 3.6 |
| Severe | 50 | 15 | 30.0 |
| With late albuminuria | 27 | 9 | 33.3 |
| Nephritis | | | |
| Mild | 121 | 19 | 15.7 |
| Moderate | 130 | 41 | 31.5 |
| Severe | 71 | 49 | 69.0 |
| Preeclampsia | 29 | 7 | 24.1 |
| Eclampsia | 63 | 26 | 41.2 |
| Nephritis or preeclampsia | 10 | 4 | 40.0 |

The group comprises 338 cases. The total number of dead babies in the group was 19 (5.6 per cent); but among the 19, two babies were congenitally syphilitic, three were born to mothers with placenta previa, one had a congenital deformity, one was a breech delivery, and one had a tight knot in the cord. That leaves eleven babies which died presumably as the result of toxemia. Two were stillborn full-term, five stillborn macerated, two were born alive and died fourteen days after birth, one premature died, and one patient aborted. The corrected deaths are 11 or 3 per cent.

*Moderate Hypertension.*—The blood pressure of the group of moderate hypertension ranges from 150 to 180 systolic and 90 to 110 diastolic. The condition may arise in a first pregnancy, but it more frequently occurs in a patient who has had mild hypertension in a previous pregnancy. The time of occurrence in pregnancy varies from the end of the first trimester to the sixth or seventh month. Once the blood pressure level has been reached it is usually maintained even in spite of treatment. After delivery the hypertension disappears, to reappear at a variable later date and, then, usually in lesser degree. The symptoms in pregnancy again are, as a rule, nil, although headaches, "spots before the eyes," and slight edema may be present. The urine is free from albumin. The blood chemistry and renal function tests are normal. The retina may be normal or may show variability of vessel contour. These patients, in spite of their hypertension, surprise us very often by their appearance of well-being.

The cases totalled 197 or 19 per cent of the entire series. The dead babies numbered 14 (7.1 per cent); but if we exclude syphilis three, fibroids one, congenital deformity one, congenital pulmonary edema one, pyelitis one, the corrected number is 7 (3.6 per cent).

*Severe Hypertension.*—A blood pressure reading of 180 to 280 systolic and 110 to 170 diastolic during a pregnancy is a source of apprehension to the attending physician. The course of the hypertension in this group differs from that of the others. Most of the patients are known hypertensives, and pregnancy is an incident. As gesta-

tion advances the blood pressure rises until when term is reached the terrifying hypertension results. These cases occur almost entirely in multiparas and one of the reasons they are not more numerous is that pregnancy is frequently terminated prophylactically. Postpartum the blood pressure comes down slightly but generally remains elevated far in excess of what it was at the beginning of the pregnancy. Symptoms directly due to the marked hypertension are usual. Edema is frequent, albuminuria is absent. The retina shows spasticity of the vessels, occasional patchy edema, and, commonly, one or two hemorrhages. Blood chemistry is not characteristic and may show either high normal figures or a slightly elevated nonprotein nitrogen and urea.

This series contains 50 cases (4.8 per cent). The dead babies number 16 (32 per cent); and if one syphilitic case is subtracted the corrected number of babies whose death is due solely to toxemia is 15 (30 per cent).

*Severe Hypertension With Albuminuria.*—Closely related to the severe hypertension group, and merging with the most severe of the next general group to be described, is a series of 27 cases (2.6 per cent of total series) which has been classified as severe hypertension showing late albuminuria. These patients run an elevated blood pressure for months. The urine gradually shows increasing albuminuria in the seventh and eighth month of gestation. Postpartum the blood pressure subsides somewhat but does not approach normal. The albuminuria persists for months. The blood chemistry taken within one to three days postpartum will show a very slight nitrogen retention. The retina shows the same changes as the severe grade of hypertension cases. Symptoms are also similar. Edema is usual and may become marked.

Nine babies (33⅓ per cent) died as the result of the toxemia.

## NEPHRITIC GROUP

The second large group, 322 cases (31 per cent), is the nephritic group which in turn is divided into mild, moderate, and severe varieties. This group is characterized by albuminuria and varying degrees of hypertension.

*Mild Nephritis.*—The criteria for the identification of the cases of mild nephritis were the following: (a) blood pressure readings 130 to 150 systolic, 80 to 100 diastolic, together with a persistent albuminuria, noted as Heavy Trace Albumin; (b) normal blood pressure with albuminuria from heavy trace to 5 per cent. Blood chemistry is normal. The eyegrounds occasionally show patchy edema. Postpartum the hypertension disappears in a day or two and albuminuria clears in a few weeks to a few months. These patients are almost entirely symptom-free except for edema. Almost all show varying grades of ankle and hand edema.

The mild type includes 121 cases (11.5 per cent), and in these there were 20 dead babies (16.5 per cent); excluding one fetal death due to congenital abnormality, the deaths due to toxemia were 19 (15.7 per cent).

*Moderate Nephritis.*—The symptoms of the moderate nephritic group may start insidiously or most acutely. The blood pressure gradually rises and, coincidentally, or more often a little later, albuminuria appears. As term approaches both hypertension and albuminuria become more marked. Symptoms that go with a corresponding mercury level appear. Edema, oliguria, and visual disturbances are common. Exposure to cold or rain may precipitate an acute onset, or such may occur without any apparent reason. In the beginning this type cannot be distinguished from the acute preeclamptic type of toxemia. The occurrence in multiparas, previous history of toxemia, presence of nitrogen retention, and the course of the disease serve to make the differential diagnosis. After a few days' bed rest and sedatives the patient quiets down and the true nature of the illness may be recognized. Postpartum

the hypertension and albuminuria persist and may not subside for many months or even years. The following types are included in this group: (a) blood pressure ranging from 150 to 180 systolic, 90 to 110 diastolic and albuminuria heavy trace to 5 per cent; (b) blood pressure 130 to 150 systolic, 80 to 110 diastolic and albuminuria from 5 to 15 per cent; (c) normal blood pressure and albuminuria 5 to 25 per cent; (d) blood pressure 130 to 180 systolic, 80 to 110 diastolic, moderate nitrogen retention (45 to 75 mg. nonprotein nitrogen), albuminuria heavy trace to 10 per cent.

The moderate nephritic group numbered 130 (12.5 per cent). The fetal deaths numbered 44 (33.8 per cent). Excluding three deaths, possibly due to syphilis, 41 cases (31.5 per cent) remain in which the cause of death was the toxemia.

*Severe Nephritis.*—The severe nephritic toxemia generally occurs in multiparas who have had preceding pregnancies with moderate toxemia or a history of a previous nephritis. Occasionally, it arises insidiously in a primipara in whom no predisposing cause can be obtained. It occurs most frequently in the early part of the second trimester and pregnancy frequently terminates about the eighth month. Postpartum the hypertension, if present, persists, and, occasionally, becomes slightly lower. The albuminuria persists for months and sometimes years; a nitrogen retention can almost always be demonstrated soon after delivery. It is generally moderate, although infrequently it precedes a terminal uremia. This is the type of case that has recurrent stillbirths about the sixth or seventh month of pregnancy. The following are the criteria: (a) blood pressure 180 plus systolic, 120 plus diastolic, and albuminuria grading from a heavy trace to a definite percentage; (b) normal blood pressure or any elevation together with an albuminuria exceeding 25 per cent; (c) normal blood pressure or any elevation, albuminuria in amounts from a heavy trace to a percentage with nitrogen retention exceeding 75 mg. per cent nonprotein nitrogen.

The severe nephritic group numbered only 71 (6.8 per cent). The number of dead babies occurring among the 71 patients was 50 (70.4 per cent); excluding one case in which syphilis was present, 49 deaths (69 per cent) resulted from the toxemia.

*Preeclampsia and Eclampsia.*—The third large group comprises the acute toxemias, preeclampsia and eclampsia. These cases start acutely in the last trimester with any of the following: visual disturbances, marked epigastric pain, nausea and vomiting, and generalized edema. The blood pressure may show a gradual rise over a two- to three-week period. Another type, coincidentally with the abruptness of the symptoms, shows a rise of pressure to 170 plus systolic and 110 plus diastolic. The urine contains albumin ranging from a "heavy trace" to a percentage. The eyegrounds are characteristic (spastic vessels, patchy edema of retina and discs, and, not too rarely, detachments of the retina). Postpartum, hypertension and albuminuria disappear very rapidly in a two-week period. The blood chemistry may show an elevation of the uric acid above 4 mg. In the next pregnancy no toxemia may be evident but, in the third and fourth, hypertension or nephritic toxemia in varying degrees of severity are apt to appear.

There were 29 cases of preeclampsia (2.8 per cent) and 63 cases of eclampsia (6 per cent), total cases 92 (8.8 per cent). Among the 29 cases of preeclampsia there were seven dead babies (24.1 per cent) whose death could be attributed only to toxemia. The relatively small number of cases in this series is due to the fact that many cases which might be classified as preeclampsia and which do not strictly follow the above description were included in the nephritic group.

Cases of eclampsia number 63 (6 per cent). The total dead babies in this series was 28 (44.4 per cent); excluding two cases (one birth injury, one congenital abnormality), the corrected number of baby deaths due to toxemia is 26 (41.2 per cent).

There is a remaining group of 10 (0.9 per cent) which cannot be definitely put in either the nephritic or preeclamptic class. The dead babies totalled 4 (40 per cent).

### INCIDENCE OF PREMATURE BIRTHS

The occurrence of prematurity in the 1,036 cases and in respect to the various types of toxemia is interesting. There were 135 cases (13 per cent) of premature birth (standard was five pounds or less birth weight, or obvious signs of prematurity). Among these, forty died before leaving the hospital. Six babies were born of syphilitic mothers of which 4 lived, and two were born of mothers having uterine fibroids. One baby died whose birth was complicated by a placenta previa. The total corrected number of premature babies, then, is due, apparently, entirely to toxemia.

Prematurity varies markedly with the individual toxemias. This point, because of the small number of cases, is brought out more clearly by percentages as in Table II.

TABLE II. INFLUENCE OF TOXEMIA ON PREMATURE BIRTH

| TYPE OF TOXEMIA | NUMBER OF CASES | CASES PREMATURITY (CORRECTED) | PREMATURITY PERCENTAGE |
|---|---|---|---|
| Hypertension | | | |
| Mild | 338 | 5 | 1.5 |
| Moderate | 197 | 9 | 4.5 |
| Severe | 50 | 5 | 10.0 |
| With late albuminuria | 27 | 12 | 44.4 |
| Nephritis | | | |
| Mild | 121 | 17 | 14.0 |
| Moderate | 130 | 33 | 25.4 |
| Severe | 71 | 26 | 36.6 |
| Preeclampsia | 29 | 7 | 24.1 |
| Eclampsia | 63 | 9 | 14.3 |
| Nephritis or preeclampsia | 10 | 3 | 30.0 |
| Total | 1,036 | 126 | |

Hypertension with late albuminuria leads all with 44.4 per cent prematurity. Although this group is the second lowest among the entire series in number, the figure must be significant especially when it is compared with the nephritic and the preeclamptic group. The negligible part played by pure hypertension, except when it reaches its highest proportions, is readily seen. Even the most severe grade of hypertension has a 4 per cent lower rate of prematurity than the mild nephritic type. The latter rises rapidly as the severity of the toxemia increases. The severe type almost triples the percentage of the mild type. A comparison of the severe hypertensive and the hypertensive patients showing albuminuria in the seventh and eighth months reveals an astounding difference of prematurity rate. The latter surpasses the former four and one-half times. The presence of albuminuria as an index of serious omen is brought out once again. These two types up until the appearance of albuminuria are extremely alike. So far it has been impossible to judge in the early months which will show albumin in the urine later. It may be that these hypertensive cases with albuminuria had better be classified in the severe nephritic group

but the hypertension is outstanding and persistent. Also the albuminuria in comparison is only temporary. These patients rarely show nitrogen retention and renal function tests at no time give evidence of failure.

The average rate of prematurity for all grades of nephritic toxemia is 25 per cent. Lowest in the mild type with 14 per cent, it climbs rapidly to 36.6 per cent in the severe. Severe nephritic toxemia and hypertensive toxemia with late albuminuria (possibly the same) have an average prematurity rate of 40.5 per cent and are the most potent in causing prematurity.

Preeclampsia leads eclampsia by 10 per cent. Several explanations might be forthcoming for this discrepancy but they would all be valueless in view of the few cases of preeclampsia presented.

The above discussion has dealt with premature babies living and dead. Further facts can be brought out by enumerating the number and percentage of premature live births only.

TABLE III

| TYPE OF TOXEMIA | NUMBER OF LIVE BIRTHS | PREMATURE LIVE BIRTHS | PERCENTAGE PREMATURE LIVE BIRTHS |
|---|---|---|---|
| Hypertension | | | |
| Mild | 319 | 4 | 1 2 |
| Moderate | 183 | 9 | 4.9 |
| Severe | 34 | 5 | 14.7 |
| With late albuminuria | 18 | 10 | 55.6 |
| Nephritis | | | |
| Mild | 101 | 11 | 10.9 |
| Moderate | 86 | 25 | 29.0 |
| Severe | 21 | 14 | 66.7 |
| Preeclampsia | 22 | 4 | 18.0 |
| Eclampsia | 35 | 4 | 11 0 |
| Nephritis or preeclampsia | 6 | 3 | 50.0 |
| Total | 825 | 89 | |

Among the 825 babies which lived, 89 (10.7 per cent) were premature. The hypertensive division again was the lowest if we exclude the group showing late albuminuria, demonstrating once more the relative innocuousness to the baby of hypertension as compared with albuminuria. If the nephritic group, 79 (corrected 76), more than doubled the hypertensive group (37, corrected 31) in total prematurity cases, and if the premature babies that died are also compared in groups, then the marked difference is sustained. The nephritic death total (27, corrected 26) was five and one-half to eight times the total of the hypertensive group (5, corrected 3); showing that nephritic toxemia has a more lethal influence on the child than hypertensive.

When the subgroups of the toxemia are compared, it is noted that the mild, moderate, and severe grades of hypertension do not show a proportionately increasing number of prematures as the grade of severity increases. In the nephritic division, a more step-like increase is seen. The preeclampsia and eclampsia groups show, too, an increased premature rate although there is apparently little difference between the two. The number of cases is very small and conclusions would only be presumptive.

If it is considered that nearly all the stillbirths and macerated fetuses credited to the entire series were also premature, then one realizes even

more strongly the etiologic factor of toxemia in the termination of gestation at the seventh and eighth month.

The occurrence of accidental hemorrhage was noted in the study. There were twenty-four cases or 2.3 per cent of the entire series. As has been described previously, no particular toxemia could be selected as a cause. The cases were distributed almost, but not quite, equally between the hypertensive and nephritic group: moderate hypertension 6, severe hypertension 2, severe hypertension with late albuminuria 2, mild nephritis 1, moderate nephritis 9, severe nephritis 4.

The development of psychoses has always been considered pertinent in a study of toxemia. There were twelve cases (1.2 per cent). Five cases occurred in the hypertensive group and seven occurred in the nephritic group.

Twins occurred in thirty-one cases. The cases were scattered but eleven occurred in the mild hypertensive group.

## DISCUSSION

DR. HENRICUS J. STANDER.—I cannot agree with the classification. It is most essential that we use a uniform classification of the toxemias. Personally, I do not like the term hypertension or essential hypertension, benign or malignant, in connection with the toxemias of pregnancy. I noticed that a large number of these cases reported tonight were grouped as hypertension, mild, moderate, and severe. I feel that some of these patients, if we study them further, may be classified as nephritic, certainly most in the group that the author calls severe hypertension with albuminuria. I believe that patients with toxemia, studied five or ten years later, or over a period of five or more pregnancies, fall into three very simple groups: first, a group which Kellogg calls recurrent toxemia, and which I have called "low reserve kidney." This is a mild type, the patients repond to treatment. In subsequent pregnancies they show no toxemia whatsoever, or they may show the same type of toxemia, and five, six, or seven pregnancies following the first, they show the same type of toxemia or none at all. The second type I feel very definitely is based on kidney damage, nephritis, and the third type is simply the so-called eclamptic group, by which I mean eclampsia and preeclampsia. I regard preeclampsia the same as eclampsia.

I feel that a great deal of confusion has been brought about by the term hypertension, and I would suggest that a national committee be appointed to make a study of the various and different classifications of toxemia to ensure one method of classification.

DR. W. W. HERRICK.—Recently with Dr. Tillman I reported results of a study in which we followed 594 cases of toxemia of pregnancy for from one to fifteen years; the average length of our follow-up being 5.6 years. Certain statistics in this group are startling. The death rate among these 594 cases is four times that expected in women of like age in this community. Eighty per cent of deaths were from causes in the cardiovascular renal field; that is, apoplexy, myocardial failure, or renal failure.

The medical man may properly say a word about the classification of toxemias of pregnancy because of their relation to certain well-known medical disorders. I agree with Dr. Stander that the nephritic group of the toxemias can be set aside as a very definite one. These are merely examples of glomerulonephritis activated or aggravated by pregnancy. They are marked by pronounced and persistent

albuminuria with or without hypertension, a tendency to nitrogen retention, to anemia, and a high fetal mortality, with a surety of recurrence in subsequent pregnancies and a comparatively short life expectancy, with death from uremia or secondary infection.

Another group of toxemias is, in our opinion, allied to hypertensive cardiovascular disease, distinct from nephritis. In this group hypertension is constant but variable. Albuminuria may be absent but when present is abrupt and late in onset and may be slight or large in amount. Nitrogen retention and anemia are absent. There is a vascular rather than an albuminuric type of retinitis. Excepting in the eclampsias there is a lesser tendency to destruction of the fetus. In the follow-up period, the clinical picture is associated with hypertensive cardiovascular disease rather than with nephritis. Death occurs from apoplexy or myocardial failure. In about 10 per cent death occurs as the result of renal arteriosclerosis rather than from primary renal inflammation as in the nephritic group. In this group we find about 80 per cent of all toxemias, including the eclampsias, preeclampsias, and the great group of milder toxemias which are nonnephritic. I believe a good inclusive term for this type is "vascular toxemia." The group of milder nonrecurring toxemias which Dr. Stander calls low reserve kidney, falls into this general vascular group and does not merit a separate classification.

The pathologist is the court of last resort. We are attempting to follow our cases to necropsy. This has been accomplished in 11 instances. In 4, a typical glomerulonephritis was found; in 7 the anatomic evidences of hypertensive cardiovascular disease, among them 3 examples of eclampsia. The remaining 4 were of the milder type often designated preeclamptic or recurring toxemia.

From our follow-up studies in 594 cases and from the limited number of necropsy findings, it seems clear to us that the vascular changes which are characteristic of eclampsia and preeclampsia may not resolve, but in about one-half of the cases continue to develop and in the course of years merge with those characteristic of hypertensive cardiovascular disease.

I agree that a reclassification of the toxemias of pregnancy is desirable. I believe it should be the joint task of the obstetrician, the internist, and the pathologist. Only on the basis of extensive clinical observation, prolonged follow-up and necropsy studies, can a logical classification be worked out. When this is done, I believe it will be found that we have two leading types of toxemia; the first, a smaller group characterized by glomerulonephritis; the second, related in etiology and course to primary cardiovascular disease with hypertension.

DR. HARRY ARANOW.—Without going into the merits of the different classifications of toxemia, one point that seems to me worth while is that it is not worth while risking the life of the mother to try to save that of the baby, because the baby so often is lost. I think when the case is serious, it is better to terminate labor without waiting too long.

DR. BENJAMIN P. WATSON.—I think the other point that arises, along the same line that Dr. Aranow referred to, is the question of terminating pregnancy early in these cases. I think we are very often hesitant in terminating pregnancy early, and in view of the figures we have had in regard to the poor chance of the child, I think those figures should help us in many cases to determine the early termination of perhaps more pregnancies than we do at present.

# AN ANALYSIS OF 127 CASES OF ECLAMPSIA TREATED BY THE MODIFIED STROGANOFF METHOD

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FROM the date of its inception in 1896 to Feb. 15, 1933, 384 cases of typical eclampsia have been observed and treated on the Obstetrical Service of the Johns Hopkins Hospital. During these thirty-six years, marked changes have occurred in the policy of the clinic in regard to the routine therapy for such patients. In the early years extremely radical procedures were employed when the convulsive attack occurred prior to delivery, accouchement forcé and vaginal hysterotomy, in later years supplemented by abdominal section. However, beginning in 1912, radical procedures were gradually given up and were supplanted by more conservative measures which did not aim at the immediate delivery of the patient. The experience of the clinic during these years and the results obtained have been well summarized in the contributions of Wilson in 1925, and Williams in 1927. On Oct. 15, 1924, a routine treatment for cases of eclampsia, new to the clinic, was instituted, the modified Stroganoff method, and this program of therapy has been consistently followed from that time to the present. The details of this treatment as employed at the Johns Hopkins Hospital were set forth in an article by Stander in 1925 and comprise essentially the conservative procedures of Stroganoff, although amended by Stander to exclude the use of chloroform and venesection.

During the eight and a third years elapsing since the institution of the above policy, 127 cases of typical eclampsia have been observed on the hospital service and uniformly treated by this method. It is believed that these cases comprise a large enough series so that the results may be analyzed and compared with those obtained with previous forms of therapy. It is also our purpose to discuss the mortality rates obtained in their relation to certain clinical phenomena occurring in the disease.

An examination of the case records of the entire series of eclamptic patients indicates that a division into four time periods so far as therapy is concerned may well be made. From 1896 to the end of 1911 the treatment was extremely "radical," as only two out of 85 patients with ante or intrapartum eclampsia were allowed to deliver spontaneously. During the next seven years a period of "transition" occurred with an ever increasing tendency toward conservative meas-

ures. From 1919 to Oct. 15, 1924, various conservative therapeutic measures were employed, but in no instance was forceful delivery of the patient carried out. This period may be termed "conservative," and it is noteworthy that liberal use of venesection was made during this time. The last period, from Oct. 15, 1924, to the present, comprises the "modified Stroganoff" era.

TABLE I. ECLAMPSIA TREATED BY MODIFIED STROGANOFF THERAPY OCT. 15, 1924, TO FEB. 15, 1933 (EIGHT YEARS, FOUR MONTHS)

CASES OF TYPICAL ECLAMPSIA, 127

| | NO. CASES | MATERNAL DEATHS | FETAL DEATHS | MATERNAL MORTALITY PER CENT | TOTAL FETAL MORTALITY PER CENT | FETAL MORTALITY EXCLUDING P. P. ECLAMPSIA |
|---|---|---|---|---|---|---|
| Total eclampsia | 127 | 14 | 50 | 11.02 | 39.37 | 51.09 |
| Mild eclampsia | 70 | 2 | 22 | 2.86 | 31.43 | 41.67 |
| Severe eclampsia | 57 | 12 | 28 | 21.05 | 49.12 | 61.36 |
| Antepartum eclampsia | 56 | 7 | 39 | 12.50 | 69.64 | |
| Intrapartum eclampsia | 36 | 2 | 8 | 5.56 | 22 22 | |
| Postpartum eclampsia | 35 | 5 | 3 | 14.29 | 8.57 | |
| Antepartum, mild | 26 | 2 | 15 | 7.69 | 57.67 | |
| Intrapartum, mild | 22 | 0 | 5 | 0.00 | 22.73 | |
| Postpartum, mild | 22 | 0 | 2 | 0.00 | 9.09 | |
| Antepartum, severe | 30 | 5 | 24 | 16 67 | 83.33 | |
| Intrapartum, severe | 14 | 2 | 3 | 14.29 | 21.43 | |
| Postpartum, severe | 13 | 5 | 1 | 38.46 | 7.69 | |

The results obtained in the treatment of eclampsia by the modified Stroganoff method are portrayed in Table I. The gross maternal mortality for the entire series was 11.02 per cent, a figure which, as will be shown subsequently, is significantly lower than that obtained under other forms of therapy.

In 1922, Thomas Watts Eden suggested that the results of treatment varied greatly with the severity of the disease and laid down the following criteria for differentiating between the mild and severe cases: (a) a temperature above 103° F., (b) a pulse rate over 120, (c) a blood pressure of 200 mm. or over, (d) an urine which solidifies on boiling, (e) absence of edema, (f) persistent coma, (g) more than ten convulsions. If two or more of the above symptoms or signs are present, the case is to be classified as severe; and as mild when none or only one of them is present. When the above cases were divided into "mild" and "severe" according to the criteria suggested by Eden, it was found that the mortality rates were 2.86 and 21.05 per cent, respectively. Only two deaths occurred among 70 cases of mild eclampsia, both of them in the antepartum variety. However, a fatal outcome ensued in more than a fifth of those cases classified as severe, and although this is an improvement as contrasted with results attained previously, yet such a mortality remains an appalling one. It is interesting to note that in contrast with an apparently widespread

belief to the contrary, postpartum eclampsia in our series resulted in a higher mortality (14.29 per cent) than either the antepartum or intrapartum types (12.50 and 5.56 per cent, respectively). As was to be expected the fetal mortality, excepting postpartum cases, was high throughout. However, it was somewhat lower than that attained previously, even under radical therapy with immediate delivery of the child.

TABLE II. RESULTS IN 384 CASES OF ECLAMPSIA

| THERAPY | | TOTAL CASES | GROSS MATERNAL MORTALITY PER CENT | GROSS FETAL MORTALITY PER CENT* |
|---|---|---|---|---|
| Period 1 | Radical 1896-1911 | 110 | 22.8 | 57.6 |
| Period 2 | Transition 1912-1916 | 71 | 16 9 | 59 6 |
| Period 3 | Conservative 1919–Oct. 14, 1924 | 76 | 14 6 | 63.9 |
| Period 4 | Stroganoff Oct. 15, 1924–Feb. 15, 1933 | 127 | 11.0 | 51 1 |

*Excluding postpartum eclampsia.

TABLE III. MORTALITY PERCENTAGE, FOUR TIME PERIODS

| | PERIOD 1 | PERIOD 2 | PERIOD 3 | PERIOD 4 |
|---|---|---|---|---|
| Total Cases | | | | |
| Mild | 10 9 | 3.4 | 0 0 | 2 9 |
| Severe | 39.1 | 26.2 | 27.5 | 21 1 |
| Total | 22.8 | 16.9 | 14.6 | 11.0 |
| Antepartum | | | | |
| Mild | 15.2 | 0.0 | 0.0 | 7 7 |
| Severe | 35 7 | 24 1 | 22.7 | 16 7 |
| Total | 24.6 | 18.9 | 11.4 | 12.5 |
| Intrapartum | | | | |
| Mild | 12.5 | 9 1 | 0.0 | 0.0 |
| Severe | 50.0 | 22.2 | 25.0 | 14 3 |
| Total | 25.0 | 15.0 | 13.3 | 5.6 |
| Postpartum | | | | |
| Mild | 0.0 | 0.0 | 0.0 | 0.0 |
| Severe | 40.0 | 56.0 | 40.0 | 38 5 |
| Total | 16.0 | 14.3 | 23.5 | 14.3 |

Tables II and III afford a comparison of the results to mother and child during the four periods of therapy as previously outlined. It will be noted that the maternal mortality rate under Stroganoff is approximately half that resulting from the old radical treatment. It is even somewhat lower than when the conservative methods in use previously were employed. A careful analysis of the case records would seem to indicate that there are only two main differences in therapy during these past two periods, namely that the use of venesection has been entirely discarded and that intravenous glucose is now rather liberally used.

Tables II and III would seem to indicate definitely the advantages of conservative over radical procedure in the treatment of eclampsia, and most particularly so far as the mild type of case is concerned.

The results in the severer cases are far from satisfactory but still represent an improvement over any line of treatment hitherto employed by us. Finally we wish to emphasize that the only type of eclampsia whose death rate remained unchanged throughout the entire period of time is the severe postpartum variety, and it is this type of case which would be least influenced by the changing methods of treatment.

The case records of those 127 eclamptic women treated by the Stroganoff method were carefully analyzed in order that the maternal mortality might be correlated with various clinical factors coincident to the condition. The results of this analysis are shown in Table IV. IV.

TABLE IV. MATERNAL MORTALITY IN TERMS OF RACE, AGE, AND PARITY OF PATIENT

| RACE | | | AGE | | |
|---|---|---|---|---|---|
| | CASES | MORTALITY PER CENT | | CASES | MORTALITY PER CENT |
| White | 61 | 13.11 | -16 yr. | 15 | 6 67 |
| Colored | 66 | 9.09 | 17-19 yr. | 40 | 5.00 |
| | | | 20-34 yr. | 54 | 20.37 |
| | | | 35 yr. and over | 18 | 0.00 |

PARITY

| | CASES | MORTALITY PER CENT |
|---|---|---|
| Para 0 | 84 | 8.33 |
| Para i and ii | 17 | 17.65 |
| Para iii, iv, and v | 18 | 22.22 |
| Para vi and over | 8 | 0.00 |

Table IV indicates the maternal mortality in terms of the race, age, and parity of the patient. It will be noted that the cases are about equally divided between the black and white races, with the maternal mortality somewhat higher in the latter group. In our experience the prognosis in eclampsia was best in the young woman under twenty years of age and pregnant for the first time. Conversely a high death rate prevailed in those patients aged twenty to thirty-four years and among multiparas of less than 6 pregnancies. It is interesting that there were eighteen cases of eclampsia without a single death in women of thirty-five years and over, eight of whom had had 6 or more previous pregnancies. Fourteen of these women returned a year or more after delivery for reexamination and all but one were found to have definite signs of chronic nephritis. It seems probable that most of the cases in this group were instances of "eclampsia superimposed on chronic nephritis," and it is our experience that the immediate prognosis in this type of case is favorable, although the remote one very gloomy.

PROGNOSIS IN ECLAMPSIA ACCORDING TO EDEN'S CLASSIFICATION

*A. Temperature and Pulse.*—That there is a direct correlation between the maternal mortality and rising temperature and pulse rate is indicated by Table V. Our experience confirms closely Eden's finding that a temperature of 103° F. and above and a pulse rate over 120 are associated with a grave prognosis to the patient.

TABLE V. MATERNAL MORTALITY IN TERMS OF TEMPERATURE AND PULSE OF PATIENT (MAXIMUM)

| TEMPERATURE | CASES | MORTALITY PER CENT | PULSE | CASES | MORTALITY PER CENT |
|---|---|---|---|---|---|
| - 99.9 | 57 | 7.02 | - 89 | 14 | 0.00 |
| 100-102.9 | 46 | 4.35 | 90-119 | 63 | 6.35 |
| 103-104.9 | 19 | 21.05 | 120-149 | 38 | 10 53 |
| 105 and over | 5 | 80.00 | 150 and over | 12 | 50 00 |

TABLE VI. MATERNAL MORTALITY IN TERMS OF BLOOD PRESSURE AND ALBUMINURIA (MAXIMUM)

| SYSTOLIC PRESSURE | CASES | MORTALITY PER CENT | DIASTOLIC PRESSURE | CASES | MORTALITY PER CENT |
|---|---|---|---|---|---|
| -159 | 11 | 0.00 | -119 | 50 | 12.00 |
| 160-179 | 35 | 5.71 | 120-139 | 53 | 15.10 |
| 180-199 | 32 | 15.63 | 140 and over | 24 | 0.00 |
| 200-219 | 28 | 21.43 | | | |
| 220 and over | 21 | 4.76 | | | |

ALBUMINURIA

| | CASES | MORTALITY PER CENT |
|---|---|---|
| Less than 1 gram | 21 | 14.29 |
| 1-9.9 grams | 72 | 5.55 |
| 10 grams and over | 30 | 10.00 |
| Unknown | 4 | ---- |

*B. Blood Pressure and Albuminuria.*—Eden stated in his classification of eclampsia that when the systolic blood pressure was over 200 mm., or the urine contained sufficient albumin to render it solid on boiling, it indicated a more serious prognosis for the given case. In this clinic it has long been the custom to estimate the amount of albumin quantitatively by the Esbach method in terms of grams per liter and also to assume that 10 grams would be the approximate equivalent of an amount necessary to render urine "solid on boiling."

Table VI shows that in our experience 180 mm. systolic pressure would afford a better dividing line between a mild or severe type of case than 200 mm. On the other hand the degree of elevation of the diastolic pressure seemed to afford no criterion as to the severity of the case. It is interesting to note that only one death occurred in 21 women whose systolic pressure was 220 or over and not a single fatal-

ity was experienced in 24 whose diastolic pressure was 140 or above. It seems probable that many of these cases were instances of the previously mentioned "eclampsia superimposed on chronic nephritis." Finally, it will be noted from Table VI that the amount of albuminuria present gave no indication of the ultimate outcome of the disease.

*C. Convulsions, Coma, and Edema.*—Table VII indicates that the prognosis of a case of eclampsia becomes grave whenever the coma is deep and prolonged or edema lacking or very slight. Furthermore it will be noted that among those 18 patients whose eclampsia was characterized by only one convulsion not a single fatality ensued. Also

TABLE VII. MATERNAL MORTALITY IN TERMS OF CONVULSIONS, COMA, AND EDEMA OF PATIENT

| COMA | | | EDEMA | | |
|---|---|---|---|---|---|
| | CASES | MORTALITY PER CENT | | CASES | MORTALITY PER CENT |
| Slight | 65 | 1.54 | None or Slight | 46 | 21.74 |
| Moderate | 30 | 3.33 | Moderate or Marked | 77 | 5.19 |
| Prolonged | 32 | 37.50 | Unknown | 4 | ---- |

CONVULSIONS

| | CASES | MORTALITY PER CENT |
|---|---|---|
| 1 | 18 | 0.00 |
| 2- 4 | 40 | 10.00 |
| 5- 9 | 31 | 9.68 |
| 10-19 | 21 | 9.52 |
| 20 and over | 17 | 29.41 |

the mortality remained unchanged and was approximately 10 per cent when from two to twenty convulsions occurred but was three times as high when the number of fits was above the latter figure.

Careful analysis of the 127 cases of eclampsia comprising this series indicates that from our experience certain modifications might be made in Eden's classification which would give a more accurate conception of the mildness or severity of a given case. Four of his criteria of severity we leave essentially unaltered; namely, prolonged coma, a pulse rate of 120 or over, temperature of 103° F. or above, and edema either absent or very slight. In our experience there was no correlation between mortality and the amount of albuminuria, and this item is omitted entirely. Furthermore we would amend the last two items so that a blood pressure of 180 and above instead of 200 be considered an indication of severity and also stipulate that 20 fits instead of 10 be made the dividing line for this item.

In order to test the validity of our proposed modification we have reexamined the case records of the last 205 eclamptic women observed in the clinic and have classified them as mild or severe according to the above schedule (Table VIII).

From Table VIII it would seem evident that the suggested modified classification affords a relatively exact fit with our experience with eclampsia treated by conservative methods.

Furthermore we have analyzed these 205 cases and related the maternal mortality to the total number of positive criteria of severity found in each instance. Those cases with none or one positive item are of course classified as mild, and in them (102) not a single maternal death occurred. However, as the number of positive criteria

TABLE VIII. RESULTS IN 205 CASES OF ECLAMPSIA ACCORDING TO PROPOSED MODIFIED CLASSIFICATION

| | CASES | MATERNAL DEATHS | MORTALITY PER CENT |
|---|---|---|---|
| Antepartum, mild | 45 | 0 | 0.00 |
| Intrapartum, mild | 29 | 0 | 0 00 |
| Postpartum, mild | 28 | 0 | 0.00 |
| Antepartum, severe | 55 | 12 | 21 82 |
| Intrapartum, severe | 24 | 4 | 16.67 |
| Postpartum, severe | 24 | 9 | 37.50 |
| Total mild eclampsia | 102 | 0 | 0 00 |
| Total severe eclampsia | 103 | 25 | 24 27 |

TABLE IX. RELATION OF RESULTS IN ECLAMPSIA TO NUMBER OF POSITIVE CRITERIA FOUND ACCORDING TO PROPOSED MODIFIED CLASSIFICATION

| POSITIVE CRITERIA | CASES | MATERNAL DEATHS | MORTALITY PER CENT |
|---|---|---|---|
| 0 | 29 | 0 | 0.00 |
| 1 | 73 | 0 | 0.00 |
| 2 | 34 | 3 | 8.82 |
| 3 | 29 | 4 | 13.79 |
| 4 | 25 | 9 | 36.00 |
| 5 | 10 | 5 | 50.00 |
| 6 | 5 | 4 | 80.00 |

TABLE X. LABOR IN ANTEPARTUM AND INTRAPARTUM CASES

| | CASES | |
|---|---|---|
| Labor spontaneous | 38 | |
| Labor operative | 48 | |
| Forceps | | 39 |
| Breech extraction | | 2 |
| Version | | 1 |
| Craniotomy | | 3 |
| Cesarean section | | 3 |
| Died undelivered | 5 | |
| Unknown | 1 | |

increase we find a rapidly rising maternal mortality rate, and it will be noted that when 4 or more factors of severity are present the mortality risk becomes 45 per cent.

Table X is included to illustrate the uniformly conservative therapy employed in the cases of the series so far as efforts at termination of the pregnancy were concerned. It should be stated that out of 56 cases of antepartum eclampsia encountered, labor was induced forty-

eight hours or more after the subsidence of the convulsive attack in 26 instances, the remaining falling into labor spontaneously. The various operative procedures detailed were of course done only after complete and spontaneous cervical dilatation had been reached. Craniotomy was employed in three instances where it seemed reasonably certain that fetal death in utero had occurred some time before. It will be noted that cesarean section was practiced on three patients, and in each case the indication for the operation was pelvic dystocia.

## SUMMARY

From Oct. 15, 1924, to Feb. 15, 1933, a total of 127 cases of typical eclampsia have been observed on the Obstetrical Service of the Johns Hopkins Hospital and routinely treated by the "modified Stroganoff" method. In this series there were fourteen maternal deaths, a mortality of 11.02 per cent. The highest death rate prevailed in the postpartum variety of the disease, and the lowest in the intrapartum. The mortality rates during the Stroganoff regime were lower than at any other period of the thirty-seven years of the clinic's existence, during which time the therapeutic policy has gradually swung from extremely radical to equally conservative methods. Indeed the death rate here given is less than half that obtained under the old radical forms of treatment. Dividing the cases into "mild" and "severe" types according to the classification of Eden, the maternal mortality was 2.86 and 21.05 per cent, respectively.

As a result of careful analysis of the above 127 cases of eclampsia, it was found that the following "modified classification" of mildness or severity in our experience gave a more exact criterion as to prognosis than Eden's original one. (1) Temperature of 103° F. or above, (2) pulse rate of 120 or over, (3) blood pressure (systolic) of 180 or over, (4) no or very slight edema, (5) deep and persistent coma, and (6) 20 or more convulsions. If two or more of these criteria occur the case is to be classified as severe.

A test of this proposed schedule in 205 consecutive cases of eclampsia resulted in 102 being classified as mild with no deaths and 103 severe with 25 deaths, or 24.27 mortality per cent. Moreover, our findings indicate a very direct correlation between the number of positive criteria of severity and the mortality risk rate.

A somewhat higher death rate was noted among the blacks than the whites in the series. Also the young woman below the age of twenty and the primipara seemed to have a more favorable prognosis than the woman in the older stages of her child-bearing career or one who had had previous pregnancies.

From the foregoing discussion it seems evident that the modified Stroganoff method offers better results in the treatment of eclampsia than any hitherto tested by us. Indeed one can safely say that in the

milder cases the results are quite satisfactory. However, in the severe type of case the mortality under this regime is still extremely high, although more favorable than under any form of treatment previously used. Obviously, as Williams has stated, "the treatment of eclampsia must remain empiric and relatively unsatisfactory until the actual cause of the disease is discovered." We believe, however, that at the present time the modified Stroganoff treatment offers as good results as any variety in vogue. Quite possibly it is little if any better than certain other essentially conservative procedures that have been suggested, such as that with magnesium sulphate. However, it seems evident that the average patient is much better off the more she is left alone. It is possible, however, that in certain of the more severe cases in which the patients seem to be becoming worse under conservative procedures, and in whom spontaneous delivery will not shortly occur, cesarean section under local or spinal anesthesia might offer more favorable results. If acidosis develops the liberal use of intravenous glucose, with or without insulin, seems definitely beneficial. In our experience, venesection is of no definite value. Finally, it seems important to avoid, so far as is possible, the use of inhalation anesthetics for any type of operative procedure which may become necessary.

## CONCLUSIONS

1. The maternal mortality in 127 cases of typical eclampsia treated by the modified Stroganoff method was 11.02 per cent. This was a lower figure than previously attained at the Johns Hopkins Hospital by other forms of therapy.

2. The maternal mortality was somewhat higher in the white than the black race. Also it was increased in the multiparous woman and in one in the older stages of the child-bearing career.

3. A modification of Eden's classification for determining the severity of a given case is suggested. This, in our experience, gave a more accurate prognosis than did the original.

4. The modified Stroganoff treatment gives quite satisfactory results in the mild form of case. In severe cases it is preferable to the old forms of radical treatment but is still followed by a high mortality, 24.27 per cent. In the latter type of case, becoming worse under conservative therapy, cesarean section under local or spinal anesthesia seems permissible.

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# STUDIES OF HEPATIC FUNCTION

## IV. Hepatic Function During Pregnancy

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STUDIES of hepatic function during normal pregnancy have yielded conflicting results. This has been particularly true of data based upon studies of the glycogenic function of the liver, the urinary nitrogen partition, and the Widal hemoclastic crisis. Many such studies have apparently indicated some degree of hepatic functional impairment in many cases but, in the light of present-day views regarding the lack of specificity of these methods, the significance of these findings is questionable. The general opinion at the present time is that the most reliable available tests of the functional capacity of the liver are those which deal with its excretory function, particularly with regard to the elimination of bilirubin and certain dyes, the one most commonly employed being bromsulphalein.

The present study consists of the determination of the serum bilirubin concentration and of the degree of bromsulphalein retention in a series of 34 normal pregnant women, 26 women with varying grades of toxemia of pregnancy and 8 presenting some other complication during pregnancy; similar studies were made in 15 of these cases twenty-four hours after delivery, in 12 instances with, and in 3 without anesthesia. The serum bilirubin determinations were made by the Thannhauser-Andersen modification of the van den Bergh procedure; as stated in a previous report,[1] in our experience the normal range of serum bilirubin is from 0.1 to 1.0 mg. per 100 c.c. by this method. The 2 mg. per kilogram dosage of bromsulphalein was employed, determinations being made thirty minutes following injection of the dye; in the absence of hepatic functional impairment, no dye should remain in the blood stream at the end of thirty minutes.

### RESULTS OF PRESENT STUDY

*Normal Pregnancy (Table I).*—In this group of 34 cases, the serum bilirubin concentration varied from 0.2 to 1.0 mg. per 100 c.c. Studies were made at term in 29 cases, during the seventh month in 2, the fifth in 1, and the third in 2 cases. Normal results were obtained with the bromsulphalein test in 26 cases, 8 showing dye retention of from 5 to 20 per cent at the end of thirty minutes. The case with

20 per cent retention was a multigravida (8) in the seventh month of gestation; the others (5 to 10 per cent retention) were studied at term, 3 being primigravidas and 4 multigravidas (2-13).

TABLE I. NORMAL PREGNANCY

| PATIENT | MONTH | GRAVIDA | SERUM BILIRUBIN (MG. PER 100 C.C.) | BROMSULPHALEIN RETENTION PERCENTAGE |
|---|---|---|---|---|
| F. S. | 3 | 2 | 0.64 | 0 |
| P. K. | 3 | 4 | 1.0 | 0 |
| H. W. | 5 | 1 | 0.4 | 0 |
| E. J. | 7 | 1 | 0.28 | 0 |
| J. J. | 7 | 8 | 0.88 | 20 |
| M. G. | 9 | 1 | 0.48 | 0 |
| H. K. | 9 | 4 | 0.56 | 0 |
| N. W. | 9 | 6 | 1.0 | 0 |
| A. P. | 9 | 2 | 0.44 | 0 |
| V. K. | 9 | 3 | 0.37 | 0 |
| B. W. | 9 | 1 | 0.37 | 0 |
| M. D. | 9 | 1 | 0.6 | 0 |
| W. Y. | 9 | 1 | 0.2 | 0 |
| V. MeC. | 9 | 1 | 0.4 | 0 |
| M. G. | 9 | 12 | 0.52 | 0 |
| F. V. | 9 | 1 | 0.35 | 0 |
| E. R. | 9 | 1 | 0.36 | 0 |
| L. R. | 9 | 1 | 0.3 | 0 |
| R. V. | 9 | 4 | 0.28 | 0 |
| A. G. | 9 | 4 | 1.0 | 0 |
| E. M. | 9 | 1 | 0.72 | 0 |
| E. W. | 9 | 1 | 0.52 | 0 |
| L. B. | 9 | 2 | 0.52 | 0 |
| A. G. | 9 | 1 | 0.56 | 0 |
| L. R. | 9 | 1 | 0.4 | 0 |
| I. K. | 9 | 9 | 0.57 | 0 |
| M. M. | 9 | 9 | 0.29 | 0 |
| C. J. | 9 | 2 | 1.0 | 5 |
| L. G. | 9 | 2 | 1.0 | 5 |
| C. Z. | 9 | 1 | 0.3 | 10 |
| B. T. | 9 | 3 | 0.24 | 10 |
| J. B. | 9 | 13 | 0.88 | 10 |
| D. D. | 9 | 1 | 0.8 | 10 |
| R. DeM. | 9 | 1 | 0.56 | 5 |

*Toxemia of Pregnancy (Table II).*—This group consisted of 2 patients with eclampsia (classified as severe toxemia), 4 with preeclamptic toxemia (classified as moderate toxemia), and 20 with mild toxemia, characterized by moderate grades of hypertension, nausea, and vomiting. In the two patients with eclampsia the serum bilirubin concentration was 1.08 and 0.8 mg., respectively, with bromsulphalein retention of 60 and 20 per cent, respectively. The four women with preeclamptic toxemia showed serum bilirubin values of 0.85, 1.2, 2.2, and 2.8 mg. and dye retention of 0, 0, 30, and 30 per cent, respectively. In the group of 20 patients with mild toxemia the serum bilirubin concentration ranged from 0.24 to 0.8 mg. per 100 c.c.; dye retention (10, 15, and 30 per cent) was present in three instances. The blood nonprotein nitrogen and blood sugar were within normal limits in every case.

*Other Complications (Table III).*—In 4 patients with chronic nephritis complicating pregnancy (NPN 49.2 to 76.4 mg. per 100 c.c.) the serum bilirubin concentration ranged from 0.54 to 1.2 mg. per 100 c.c.; dye retention (5 per cent)

TABLE II. TOXEMIA OF PREGNANCY

| PATIENT | MONTH | GRAVIDA | SERUM BILIRUBIN (MG. PER 100 C.C.) | BROMSULPHALEIN RETENTION PERCENTAGE | CONDITION |
|---|---|---|---|---|---|
| C. H. | 9 | 1 | 1.08 | 60 | Severe |
| E. K. | 9 | 1 | 0.8 | 20 | Severe |
| E. C. | 3 | 7 | 0.85 | 0 | Moderate |
| M. M. | 5 | 9 | 1.2 | 0 | Moderate |
| M. R. | 7 | 1 | 2.8 | 30 | Moderate |
| K. M. | 3 | 2 | 2.2 | 30 | Moderate |
| G. P. | 6 | 1 | 1.00 | 0 | Mild |
| M. B. | 7 | 4 | 0.4 | 0 | Mild |
| V. N. | 7 | 2 | 0.66 | 0 | Mild |
| E. S. | 9 | 2 | 0.33 | 0 | Mild |
| A. G. | 9 | 6 | 0.36 | 0 | Mild |
| J. W. | 9 | 2 | 0.36 | 0 | Mild |
| R. R. | 9 | 8 | 0.24 | 0 | Mild |
| A. Si. | 9 | 1 | 0.25 | 0 | Mild |
| A. St. | 9 | 3 | 0.52 | 0 | Mild |
| M. S. | 9 | 1 | 0.76 | 0 | Mild |
| O. E. | 9 | 2 | 0.29 | 0 | Mild |
| C. M. | 9 | 1 | 0.66 | 0 | Mild |
| M. J. | 9 | 8 | 0.52 | 0 | Mild |
| M. H. | 9 | 4 | 0.56 | 0 | Mild |
| R. R. | 9 | 4 | 0.56 | 0 | Mild |
| A. M. | 9 | 10 | 0.25 | 0 | Mild |
| E. B. | 9 | 6 | 0.8 | 0 | Mild |
| C. H. | 9 | 4 | 0.35 | 15 | Mild |
| L. P. | 9 | 3 | 0.52 | 30 | Mild |
| C. S. | 9 | 1 | 0.38 | 10 | Mild |

TABLE III. COMPLICATED PREGNANCY

| PATIENT | MONTH | GRAVIDA | SERUM BILIRUBIN (MG. PER 100 C.C.) | BROMSUL-PHALEIN RETENTION PERCENTAGE | CONDITION |
|---|---|---|---|---|---|
| R. O. | 9 | 9 | 0.88 | 0 | Chronic nephritis |
| E. K. | 7 | 12 | 0.6 | 5 | Chronic nephritis |
| A. C. | 9 | 5 | 0.54 | 5 | Chronic nephritis |
| R. M. | 9 | 1 | 1.2 | 0 | Chronic nephritis |
| L. P. | 9 | 2 | 0 35 | 5 | Pyelitis |
| V. S. | 9 | 8 | 0.5 | 15 | Pyelitis |
| M. T. | 4 | 4 | 0.71 | 5 | Carcinoma of ovary |
| G. B. | 6 | 2 | 0.25 | 0 | Syphilis |

was present in 2 of these cases. In 2 patients with pyelitis the serum bilirubin was 0.35 and 0.5 mg. per 100 c.c., with dye retention of 5 and 15 per cent, respectively. One patient with carcinoma of the ovary had a serum bilirubin concentration of 0.71 mg. with dye retention of 5 per cent and in one with tertiary syphilis the serum bilirubin concentration was 0.25 mg. per 100 c.c., with no dye retention.

*Effect of Delivery and Anesthesia (Table IV).*—Studies were made in 15 cases before and twenty-four hours after delivery. In 3 instances no anesthetic was employed; the serum bilirubin concentration was unchanged in 1, rose slightly in 1, and fell slightly in the other. In 1 case with 60 per cent retention of bromsulphalein antepartum (eclampsia), there was only 30 per cent retention after delivery. The details regarding the type and quantity of anesthetic administered to the other patients in this group are presented in Table IV. The serum bilirubin concentration

rose appreciably in 5 cases, fell appreciably in 4, and remained essentially unchanged in 3 instances; in no patient receiving an anesthetic, however, was it above the upper limit of normal either before or after delivery. In 1 case (L. R.) with no antepartum retention of bromsulphalein, 60 per cent retention was present postpartum. In 2 others (E. K. and B. T.) with 20 and 10 per cent retention antepartum, respectively, this retention was increased to 80 and 15 per cent after delivery. Two others (J. B. and C. Z.) with 10 per cent retention and the remaining 7 with no retention remained unaltered.

TABLE IV. EFFECT OF DELIVERY AND ANESTHESIA

| PATIENT | ANESTHESIA | DELIVERY | SERUM BILIRUBIN (MG. PER 100 C.C.) | | BROMSULPHALEIN RETENTION PERCENTAGE | |
|---|---|---|---|---|---|---|
| | | | BEFORE | AFTER | BEFORE | AFTER |
| C. H. | None | Spont. | 1.08 | 0.96 | 60 | 30 |
| R. R. | None | Spont. | 0.24 | 0.24 | 0 | 0 |
| V. McC. | None | Spont. | 0.4 | 0.68 | 0 | 0 |
| V. K. | Chlorof. 20 minims | Spont. | 0.37 | 0.82 | 0 | 0 |
| A. P. | Chlorof. 20 minims | Spont. | 0.44 | 0.3 | 0 | 0 |
| B. W. | Chlorof. 30 minims | Spont. | 0.37 | 0.39 | 0 | 0 |
| E. K. | Chlorof. 240 minims | Forceps | 0.8 | 0 68 | 20 | 80 |
| J. W. | Chlorof. 30 minims | Spont. | 0 36 | 0 35 | 0 | 0 |
| J. B. | Chlorof. 60 minims | Spont. | 0.88 | 0.56 | 10 | 10 |
| C. Z. | Chlorof. 240 minims | Forceps | 0.3 | 0 65 | 10 | 10 |
| L. R. | Chlorof. 60 minims | Forceps | 0.3 | 0.78 | 0 | 60 |
| W. Y. | Chlorof. 60 minims | Forceps | 0.2 | 0.44 | 0 | 0 |
| M. G. | Ether ½ oz. | Spont. | 0.48 | 0.35 | 0 | 0 |
| B. T. | Ether 8 oz. | Section | 0.24 | 0.44 | 10 | 15 |
| G. B. | Ether 10 oz. | Forceps | 0.25 | 0.29 | 0 | 0 |

## DISCUSSION

Several authors, including Schmidt,[2] Mikeladse,[3] Breda[4] and Eufinger and Bader,[5] believe that normal pregnancy is accompanied by a mild degree of hyperbilirubinemia. However, the values reported by these observers are rarely above 0.7 mg. per 100 c.c. and should, in our experience, be considered to be within normal limits. Murchison[6] believed that pressure of the gravid uterus upon the extrahepatic bile ducts might cause hyperbilirubinemia, but this seems highly improbable. Westphal[7] suggested that a state of physiologic vagotonia may exist during pregnancy and that the heightened excitability of the vagus may produce spasm of the bile ducts, biliary stasis, and hyperbilirubinemia. As stated by Barron,[8] these theoretical concepts have received no experimental or clinical support. The data reported here support the belief that the serum bilirubin concentration remains within normal limits during the course of normal pregnancy.

In spite of this and similar observations, however, there is some rather definite evidence that the capacity of the liver for eliminating bilirubin is somewhat diminished during the period of gestation. Kaufmann[9, 10] found that 8 of 16 women showed an abnormal delay in the excretion of intravenously injected bilirubin. Soffer[11] studied 21 normal pregnant women by the same method, i.e., the bilirubin excretion test. Eleven of these were studied during the first four months of gestation, only 1 of whom showed an abnormal response. On the other hand, abnormal findings were obtained in 9 of 10 women studied during the last five months of pregnancy. Of 10 patients studied during both the first and the second half of pregnancy, 8 showed increased delay in the elimination of bilirubin during the latter period. Hyperbilirubinemia was apparently not present in any case in this series.

As stated previously, other tests of hepatic function have yielded conflicting results. Walthard,[12, 13] investigating the degree of urobilinuria, among other things, concluded that there is some impairment of liver function during labor but not during pregnancy. Rosenfeld and Schneiders[14] obtained normal results with the phenoltetrachlorphthalein test in 6 normal pregnant women, while Smith[15] reported occasional slight dye retention in a group of 20 normal pregnant women. Normal findings were obtained with the bromsulphalein test by Siegel[16] in 62 patients and by Freiheit[17] in 20 cases, the latter being in the last month of pregnancy. In the present series of 34 normal cases, retention of bromsulphalein of from 5 to 20 per cent was observed in 8 instances (23.5 per cent). This comparatively high incidence of hepatic functional impairment is probably due to the relatively small number of cases in this group, but the same may be said of the negative findings reported by other observers. Although of no real statistical value, these observations are, we feel, of definite significance so far as they add material support to the belief in the existence of some disturbance of hepatic function during the latter half, at least, of normal gestation. It may be mentioned that Huwer[18] states that hepatic function tests based on the ability of that organ to eliminate dyes are not applicable during pregnancy because of alterations in the protein content of the blood plasma. In our opinion, however, there is no substantial evidence that the latter factor exerts any significant influence upon the elimination of bromsulphalein.

The majority of investigators of this subject agree that some disturbance of liver function, if not actual liver damage, is a common manifestation of the toxemia of pregnancy. There seems little doubt that the severe forms of this condition, commonly designated eclampsia gravidarum, are associated with, if not dependent upon, varying degrees of acute or subacute hepatic necrosis. According to Hofbauer,[19, 20] as a result of increase in the size of the gravid uterus, there develop (1) stasis in the central veins of the liver lobules, (2) disappearance of glycogen and its replacement by fat droplets, and (3) biliary stasis. He believes that these changes are accompanied by evidence of hepatic functional impairment, as indicated by urobilinuria, alimentary levulosuria, and delayed elimination of intravenously injected bilirubin. These changes, constituting what Hofbauer terms the "liver of pregnancy," represent, according to him, the initial anatomic basis for the development of eclampsia. Similarly, Paramore[21] believes that marked dilatation of the venules of the hepatic lobules, particularly the central veins, constitute the fundamental pathologic lesion of eclampsia. It is doubtful, however, that marked circulatory changes in the liver can result merely from the increased intraabdominal pressure caused by the gravid uterus.

Eufinger and Bader[5] reported a positive direct van den Bergh reaction in 8 of 20 cases of hyperemesis gravidarum and in 8 of 15 cases of eclampsia. Barron[8] states that all authors agree that the estimation of the serum bilirubin concentration in such patients is of great prognostic value since the degree of hyperbilirubinemia parallels the gravity of the symptomatic manifestations. Heynemann[22] advised that all pregnant women with serum bilirubin concentrations above 1 mg. per 100 c.c. should be watched carefully. In the present series there were 20 patients with mild toxic manifestations consisting of slight hypertension, moderate nausea and vomiting, albuminuria and, occasionally, edema. The serum bilirubin concentration was within normal limits in every case. Hyperbilirubinemia was present in 3 of 4 cases regarded as moderately toxic (preeclamptic) and in 1 of 2 cases of eclampsia. Contrary to the statement made by Barron, there was no apparent relationship between the degree of bilirubinemia and the severity of the toxic manifestations. The direct van den Bergh reaction was negative in every instance.

Several authors have emphasized the value of the bromsulphalein and other dye tests in the diagnosis of the toxemias of pregnancy. Smith[15] reported impairment of elimination of phenoltetrachlorphthalein in 20 of 44 toxic patients; he concluded that dye retention indicates severe toxemia but that the degree of retention is not proportional to the extent of liver damage. A similar opinion was expressed by Naujoks.[23] Krebs and Dieckmann[24] obtained variable findings in a group of 37 women with toxemia of pregnancy, none of whom was suffering with eclampsia. The majority showed a moderate degree of dye retention, some showed no retention, and a few were markedly abnormal. Positive findings were usually obtained in two types of patient: (1) those with hypertension but no toxic symptoms and (2) those with toxic symptoms but no hypertension. Rosenfeld and Schneiders[14] reported dye retention in 7 patients with hyperemesis gravidarum and in 9 with hypertension. King[25] made the following observations regarding bromsulphalein retention in the toxemia of pregnancy: (1) no retention in 11 cases without convulsions; (2) from a trace to 25 per cent retention in 7 of 10 cases of eclampsia; (3) from 10 to 25 per cent retention in 3 cases of hyperemesis gravidarum. Trainor[26] noted dye retention in 2 women with postpartum eclampsia. Siegel[16] reported the following findings: from 1 to 3 per cent bromsulphalein retention in 17 toxic patients without hypertension; from 1 to 3 per cent retention in 6 cases of eclampsia; very slight retention (1 per cent) in 2 patients with hyperemesis gravidarum. The following observations were made by Freiheit[17]: of 7 patients with hyperemesis gravidarum, 2 showed dye retention, one with 10 per cent retention dying in four weeks with acute yellow atrophy of the liver, the other, with 20 per cent retention, giving a normal response three days postpartum; of 13 cases with hypertension, albuminuria, and edema (kidney of pregnancy), 4 showed a trace and 2 showed 5 per cent retention; of 11 cases with convulsions, 3 showed 15 per cent and 1 showed 20 per cent retention. Freiheit concluded that whereas this procedure may be of value in determining the degree of toxemia in hyperemesis gravidarum, it is not of value either in predicting the outcome or in differentiating nephritic from eclamptic toxemia. In this latter statement he differs from the majority of authors who believe that dye retention is usually present in eclampsia and is uniformly absent in nephritis.

In the present series, retention of bromsulphalein (20 and 60 per cent) was present in both patients with eclampsia, in 2 of 4 moderately toxic patients (30 per cent), and in 3 of 20 mildly toxic patients (10, 15, and 30 per cent). All patients recovered. Retention of 5 per cent was also noted in 2 of 4 cases of chronic glomerulonephritis complicating pregnancy; these two patients presented rather marked nitrogen retention (71.2 and 76.4 mg. N.P.N. per 100 c.c.) and were quite toxic. We have obtained similar findings in a number of nonpregnant patients with renal failure and believe that dye retention under such circumstances is dependent upon hepatic functional impairment which may be either "functional" or organic in origin. This problem is under investigation at the present time. However, the absence of any evidence of renal functional impairment in patients with eclampsia is usually of great practical value in differentiating between that condition and glomerulonephritis complicating pregnancy. It should be noted, however, as pointed out by Cantarow and Ricchiuti,[27] that the urea clearance test cannot be relied upon in the estimation of renal functional efficiency during the latter months of gestation. In 2 cases of pyelitis and 1 of carcinoma of the ovary with dye retention, the presence of hepatic disease was not ruled out. The data presented here would appear to suggest that although hepatic functional impairment, as evidenced by bromsulphalein retention, is more consistently present in severe than in mild forms of toxemia of pregnancy, the presence or degree of

dye retention bears no direct relation to the severity of the toxemia. They further demonstrate the observation made elsewhere[1, 28] that dye retention may be present in the absence of hyperbilirubinemia, and vice versa. It is of interest to note that in one case (K. M.) the degree of dye retention dropped from 30 per cent to 7 per cent in twenty-four hours, suggesting that the hepatic functional impairment was perhaps not due entirely to organic or structural changes in the liver.

The data presented in Table IV dealing with the effect of delivery and anesthesia are self-explanatory. One of the three patients receiving no anesthetic (C. H.), with 60 per cent dye retention, showed only 30 per cent retention twenty-four hours following delivery. This patient was suffering with eclampsia, and the apparent rapidity of improvement of liver function suggests, as in the case cited above, that a large part of the hepatic disturbance rests upon a nonorganic basis. Three of the patients who received an anesthetic during labor showed increased dye retention after twenty-four hours; only 1 of these had no dye retention before delivery (L. R.). Of the 4 patients with antepartum dye retention receiving an anesthetic, no increase was noted in 2 cases, slight increase (5 per cent) in 1 (B. T.), and marked increase (60 per cent) in the other (E. K.). This increase was a temporary one, normal findings being obtained in all cases after four days. On the basis of our experience with regard to the effects of anesthesia upon bromsulphalein retention, to be reported later, it would appear that impairment of dye elimination by the liver is more readily produced by anesthetic agents in the pregnant than in the nonpregnant state. They should be employed with particular caution in the presence of evidence of hepatic functional impairment.

## SUMMARY

1. In a group of 34 normal pregnant women, the serum bilirubin concentration ranged from 0.2 to 1.0 mg. per 100 c.c. Normal results were obtained with the bromsulphalein test in 26 cases; one case showed 20 per cent retention and 7 showed from 5 to 10 per cent retention.

2. Similar studies were performed upon 26 women with toxemia of pregnancy. In 2 cases of eclampsia the serum bilirubin concentration was 1.08 and 0.8 mg. per 100 c.c., and there was bromsulphalein retention of 60 and 20 per cent, respectively. Hyperbilirubinemia was noted in 3 and dye retention (30 per cent) in 2 of 4 patients with a moderate grade of toxemia. Dye retention (from 10 to 30 per cent) was present in 3 of 20 cases of mild toxemia, all of whom presented normal serum bilirubin values.

3. Dye retention (5 per cent) was found in 2 of 4 pregnant women with advanced chronic glomerulonephritis and renal failure, in one with carcinoma of the ovary (5 per cent), and in 2 with pyelitis (5 and 15 per cent, respectively).

4. Studies were made in 15 cases before and twenty-four hours after delivery. An increase in the degree of bromsulphalein retention was noted in 3 patients, all of whom had received an anesthetic at the time of delivery. The serum bilirubin concentration rose in 6 cases, fell in 5, and remained practically unchanged in 4 cases. It appears that impairment of dye elimination is more readily produced by anesthetic agents in the pregnant than in the nonpregnant state.

5. These data suggest that although the serum bilirubin concentration remains within normal limits during normal pregnancy, some degree of hepatic functional impairment is present in a not inconsiderable proportion of cases. The degree of demonstrable impairment of hepatic function in patients with toxemia of pregnancy does not parallel the severity of the toxic manifestations. Studies of hepatic function are, however, of considerable diagnostic value in this connection.

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**Hermstein, A.: The Natural Variations in Female Fertility,** Med. Klin. **29:** 899, 1933.

Some authors contend that there is a physiologic period of sterility in women whereas others deny this. This question can only be answered by determining definitely how long spermatozoa are capable of fertilization, how long ova may remain alive, and the period of ovulation. It is generally conceded that spermatozoa, while they may remain alive for as long as three and a half weeks, are not capable of fertilization for more than forty-eight hours. Ova most likely have a still shorter capability of fertilization. However, the knowledge we have of these germ cells in the human being is very scanty. The period of ovulation in women has not definitely been decided; however, the general consensus of opinion is that ovulation occurs between the fourteenth and sixteenth days. As Ogino points out we should calculate the date of ovulation from the menstrual period which follows and not from the menses which precedes ovulation because ovulation determines the next menstrual period and has nothing to do with the past flow of blood. Ovulation according to Ogino occurs from the twelfth to the sixteenth day before the next menstrual period.

# LABOR IN THE CARDIAC PATIENT*

## With a Report of the Occurrence of Coronary Occlusion in Pregnancy and Labor

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THE association of heart disease and pregnancy is of serious import to the patient. The immediate and remote prognosis is frequently uncertain. The course of the cardiac patient who becomes pregnant must be guided by intelligently planned cooperation between internist and obstetrician.

To approach this problem correctly there must be a complete revision of the prevalent ideas concerning the interrelationship between pregnancy and heart disease. Medical literature is replete with reports and discussions based on the theory that the pregnancy is the primary condition and that the cardiac pathology is the complication. In the light of present knowledge the existing cardiac disease must be regarded as primary and the pregnancy as the complication. Daly and Strouse[3] have stated the problem most accurately: "A woman with organic heart disease who becomes pregnant is immediately treated as a case of pregnancy with medical complications. This position is no longer tenable. The medical side of the complication must become the paramount issue, the pregnancy the complication."

While pregnancy becomes less ominous to the cardiac patient with such a change in attitude, when superimposed it presents certain definite problems. Pregnancy places a mechanical burden upon the heart because of the increase in blood flow, blood volume, and the work of the entire circulatory apparatus. Recent studies show the increase in outflow[14] to be as much as 25 per cent by the fourth month of pregnancy, and 50 to 60 per cent at term. The increase in blood volume[12] is 6 to 9 per cent of the body weight, the actual gain being 400 to 500 gm. The important factors to be considered are, first, this additional work during pregnancy and second, the effect of labor upon the cardiac patient.

*Frequency.*—This study was undertaken to determine the effect of labor upon the cardiac patients who were delivered in the Department of Obstetrics in the Michael Reese Hospital. There were 7,670 patients delivered during the five years ending April 10, 1934; 102 of these, 1.33

*Read at a meeting of the Chicago Gynecological Society, May 18, 1934.

per cent, had definite cardiac pathology. Reports in the literature as to the frequency of cardiac pathology vary from 4.15 per cent (Stander[16]), 2.7 per cent (Lamb[10]) and 1.11 per cent (Carr and Hamilton[2]) to 0.25 per cent (in the survey made by Sparks[17]), 0.25 per cent (Daly[3]) and 0.16 per cent (FitzGibbon[4]).

In addition 765, or 9.85 per cent, had various types of cardiac murmurs during pregnancy, but showed no signs of heart disease. The frequency of these functional types of murmurs has been variously reported. Lamb[10] found 6.1 per cent; Hamilton and Kellogg,[7, 8] 7.5 per cent. MacKenzie[11] has shown very definitely that this type of murmur in pregnancy is without significance and should have no bearing on the conduct of labor.

Another type of functional disturbance of the heart which is found frequently during pregnancy is the occurrence of extrasystoles. These are usually transient, but occur with increasing frequency in the last trimester of pregnancy. They are of no significance without other evidence of cardiac pathology and practically always disappear after labor.

*Cardiac Pathology.*—Analysis of the types of cardiac pathology found in the 102 patients in this series shows a preponderance of rheumatic heart disease; 86 patients, 85 per cent, had mitral disease. Others have reported this same high incidence of mitral disease of rheumatic origin.[1, 2, 5, 6, 15, 17] In 69 of these, the diagnosis was mitral stenosis and regurgitation. Mitral stenosis alone was found in 11, and mitral regurgitation alone in 6. Two women had, in addition to the mitral disease, definite involvement of the aortic valves, one patient had a partial heart-block due to digitalis and one patient showed a partial heart-block and auricular fibrillation in addition to the mitral disease.

Only six patients in this group showed evidences of decompensation at the time of labor. One patient had congenital syphilis, a marked hyperthyroidism and a lipoid nephrosis. She was delivered of a sympus apus.[13] Another patient had, in addition to her mitral disease, a typical chorea gravidarum. She had a mild decompensation during pregnancy.

Twelve patients showed evidences of myocardosis, two being in association with long-standing, severe hyperthyroidism, two in association with arteriosclerosis, and two secondary to nephritis. Only one of these twelve suffered decompensation during pregnancy or labor. The clinical course of this patient was so unusual that it merits a detailed report.

Mrs. N., forty-five years of age, a gravida vi, para iv, was admitted to the gynecologic service Oct. 10, 1933, in her fourteenth week of pregnancy for therapeutic abortion and sterilization, because of a chronic myocardosis, arteriosclerosis, and hypertension (210/140) complicated by a nephrosclerosis. The husband and one living child being definite syphilitics, the patient was placed on the usual antisyphilitic treatment in spite of repeated negative Wassermann and Kahn reactions. She was discharged after one week, having refused to permit the pregnancy to be

terminated. She was readmitted when thirty-four weeks pregnant with marked evidences of decompensation in spite of close medical observation in the outpatient department. At this time her systolic pressure was 166. With prolonged rest in bed and appropriate therapy her blood pressure rose to its former level (210/120). On April 2, 1934, while still in the hospital, she developed a coronary occlusion with moderate heart failure. She recovered from this attack and on April 4, 1934, the membranes ruptured spontaneously, following which she had a second coronary occlusion with symptoms less marked than in the initial attack. During this time the pregnancy was ignored, in spite of the fact that she was at term and that the membranes had ruptured spontaneously. Forty hours after the rupture and the second occlusion, labor set in. She was given morphine at fre-

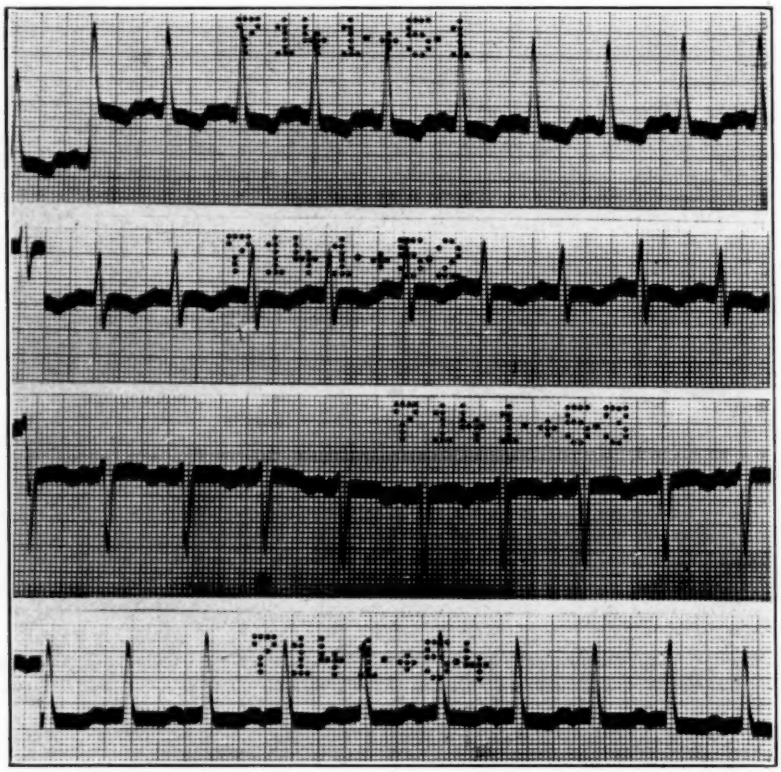

Fig. 1.—Rate 100. P-R interval 0.16 sec. S-$T_{1,2}$ negative. $T_2$ is now definitely inverted. $T_3$ is flatter. $T_4$ is much smaller and tends to be diphasic. Sinus tachycardia. Changes since last record strongly suggest a recent coronary occlusion.

quent intervals and after eleven hours of labor, cervical effacement and dilatation being completed, labor was terminated by low forceps extraction to eliminate the second stage. Her immediate convalescence has been entirely uneventful.

As far as can be determined from a search of the literature, the recognition of this occurrence of coronary occlusion in pregnancy or labor is unique.

Other cardiac pathology included myocardosis, 12; with hyperthyroidism 2, arteriosclerosis 2, nephritis 1, auricular fibrillation 1, nephro-

sclerosis and coronary occlusion 1. Congenital heart lesions were found in 3 cases, and auricular fibrillation in 1. None of these had any cardiac embarrassment during pregnancy or labor.

*Parity.*—The clinical course of the cardiac patient during the period subsequent to her last pregnancy should afford an index of her safety in further pregnancies. The fact that a damaged heart will go through pregnancy and labor without symptoms and without any evidence of cardiac embarrassment or failure should not be taken as a criterion for subsequent pregnancies. Scott and Henderson[15] have pointed out the fact that while a patient may stand pregnancy and labor uneventfully as a primipara, she may die some years later of a failure in a second pregnancy. This fact is especially important since the majority of patients suffer from mitral disease of rheumatic origin, a condition which is notoriously progressive.

On the other hand it is of interest to note the fact that many patients with definite rheumatic mitral disease go through repeated pregnancies with apparently no ill effects. It must be assumed that the cardiac pathology in these patients is stationary rather than progressive. It must further be assumed that there was practically no myocardial damage in any of this group since cardiac efficiency is dependent upon the condition of the myocardium rather than upon the valvular lesion. Of the patients in this series 34 were primiparas, 24 were in their second pregnancy, 16 in their third, and 13 in their fourth. Of the remaining 15 patients, 12 suffered from mitral lesions of rheumatic origin; 5 were in their fifth, 2 in their sixth, 2 in their seventh, 2 in their eighth, 2 in their ninth, 1 in her eleventh, and 1 in her seventeenth pregnancy.

It has been shown previously that a large percentage of cardiac patients do not carry to full term, a fact which should be beneficial. In this series 75 patients (74 per cent) carried to term. One patient carried four weeks past her calculated date. Of the remainder, 24 (22 per cent) were delivered between the twenty-eighth and thirty-eighth week of pregnancy. In seven of these labor was induced, the remainder, 16, had spontaneous premature labor.

*Length of labor.*—It has frequently been stated that spontaneous labor is more rapid in the cardiac patient than in the noncardiac. This has been explained by the fact that the increased edema of the soft parts and especially of the cervix tends toward rapid effacement and dilatation and an increased rate in the descent of the fetal head. Labor should be shorter than average in a group of cardiac patients. This is borne out by an analysis of the length of labor in this series. The average length of the first stage of labor in the primiparas was eleven hours and three minutes, and in multiparas was six hours and thirty-five minutes. The average total length of labor for the primiparas was twelve hours and for the multiparas, seven hours and twenty-four minutes.

*Conduct of labor.*—The cardiac patient who becomes pregnant must have careful medical supervision throughout her pregnancy. Such care includes restriction of activity and proper medication as indicated. The all important factor for the cardiac patient whose heart is tottering on the brink of decompensation is the proper restriction of activities and her ability to carry out such enforced rest. Here the social status plays a rôle. The cardiac patient of means can insure the maintenance of her cardiac compensation to a large extent by prolonged rest. The working woman who must continue her household duties is apt to decompensate much more frequently. Scott and Henderson[15] have shown that cardiac failure during pregnancy is twice as frequent among service patients as in a private clientele. In order that the morbidity and mortality in the two groups will be the same, service patients must have available the same opportunity for necessary rest as do the private patients.

Under ideal conditions the cardiac patient will, in the vast majority of instances, begin her labor with cardiac compensation and with the necessary cardiac reserve. These must be maintained throughout the first stage of labor by the adequate use of morphine, sedatives, or various analgesics. The use of morphine still furnishes the best means of insuring rest during labor; morphine also is of inestimable value for resting the damaged heart. Therefore, the liberal use of morphine is doubly indicated for the cardiac patient.

A definite amount of muscular effort is required to complete the second stage of labor spontaneously. It is generally considered that the repeated effort of bearing down is too great a strain to place upon an already diseased heart; hence the admonition in practically every discussion on this subject in the literature that the second stage of labor must be eliminated. In the abstract, this would seem to be correct. Since the amount of muscular work entailed upon the patient in completing the second stage spontaneously is dependent upon a combination of many factors such as multiparity, size of the fetus, pelvic measurements and condition of the soft parts, it would not seem judicious to generalize too completely. As is shown, the majority of the women in this series had short and comparatively easy second stages ending in spontaneous delivery. Only 65 per cent required anesthesia. Five women in this series had multiple pregnancies. These five sets of twins were delivered spontaneously without any great effort on the part of the patient because of the fact that these fetuses were smaller than average.

Of the twenty-six primiparas who were delivered vaginally, 12 had spontaneous deliveries, 11 were terminated by low forceps, 1 by mid-forceps, 1 by version and extraction and 1 by manual aid of a breech presentation. Of the fifty-six multiparas who were delivered vaginally only 9 required low forceps, 1 a version and extraction, and 1 manual aid of a breech presentation.

*Anesthesia.*—As stated above, 35 per cent were allowed to deliver without anesthesia. It has been the experience at the Michael Reese Hospital that ethylene is a perfectly safe anesthetic for the cardiac patient, and is the anesthetic of choice. Of the 65 patients requiring anesthesia, 43 had ethylene, 3 had ethylene and ether, and 7 had ether alone. In these latter the ether was administered by the house staff at a time when no anesthetist was available, only the full-time anesthetists being allowed to administer ethylene. Eleven of the patients were delivered by cesarean section under local anesthesia, and two under spinal anesthesia.

*Third Stage of Labor.*—The third stage of labor carries a small, but very definite risk for the cardiac patient. The more or less sudden decrease in intraabdominal pressure coupled with the lowering of the diaphragm and the abrupt change in the cardiac axis are all factors which can lead to cardiac collapse. This is well illustrated, first, by the case previously reported in detail in which rupture of the membranes was immediately followed by a coronary occlusion, and, second, by one fatality in this series which will be described later. This second patient also showed postmortem evidence of coronary disease.

In an attempt to obviate the sudden disasters which have been reported in the third stage, it has been the routine for many years in the Michael Reese Hospital to place sandbags on the abdomen concurrently with the expulsion of the child. It is worthy of note in this connection that in the two fatalities in this series this routine was not carried out. In the remaining 100 patients there were no accidents in connection with the third stage, and in none was there any break in compensation either during this stage or in the puerperium.

*Cesarean Section.*—Of the 102 patients, 20 were delivered by cesarean section. This is too high an incidence. It should be noted that 9 sections were performed for strictly obstetric indications and were not done because of the cardiac pathology. The indications in 4 of these were acute fulminating toxemia of pregnancy; 2 were done for disproportion after fourteen- and twenty-one-hour tests of labor, respectively; 1 was for chorea gravidarum; 1 was a repeat cesarean section; and 1 for placenta previa.

The cardiac condition was given as the indication in the remaining 11 patients. In 10 of these, sterilization was included as part of the operative procedure. This incidence of over 10 per cent of cesarean section for cardiac disease is still too high. They were considered justifiable because of the fact that sterilization was included in 10. Ideally it would seem better to have the cardiac patient deliver vaginally and return subsequently for sterilization. Experience has shown, however, that the majority of these patients do not return unless they become pregnant again. They will then require therapeutic abortion and sterilization. This latter procedure is less of a physical insult than cesarean section at term. The tendency in recent years at the Michael Reese

Hospital has been away from cesarean section as the ideal method of delivering the cardiac patient. The desire to sterilize the patient should not sway the obstetrician.

*Toxemia.*—There seems to be a definite increased incidence of the toxemias of pregnancy in cardiac patients. This has been previously noted by Corwin[1] and his group, who found an incidence of 19.4 per cent in the cardiac group as compared with 6 per cent in the noncardiac group. In this series 25 of the 102 patients showed definite evidence of toxemia, 24.5 per cent. This includes one patient with chorea gravidarum. During this same period at the Michael Reese Hospital, the incidence of toxemias of pregnancy for all patients was 7 per cent.

*Mortality.*—There were two deaths in this series, a mortality rate of slightly less than 2 per cent.

One patient, a twenty-six-year-old primipara, had a mitral regurgitation of rheumatic origin. She gave no history of decompensation nor was there any evidence of heart failure at any time. Her blood pressure ranged from 120 to 140 during pregnancy and was 150/68 on admission. Labor was induced at term by giving castor oil and stripping of the membranes. The first stage lasted nineteen hours and thirty minutes, during which time she was given two periods of rest by means of morphine. After being in the second stage under ethylene analgesia for fifty minutes the fetal head was still above the level of the ischial spines and the position was L.O.T. At this time a version and extraction was performed under ether anesthesia for failing fetal heart tones. A living female child was obtained. The placenta was delivered spontaneously after eight minutes. Twenty minutes later she became cyanotic and dyspneic with rapid shallow breathing. Her pulse rate jumped to 160 and she soon showed signs of pulmonary edema. Repeated hypodermic injections of morphine and atropine, and intravenous injections of digalen were administered without avail. Death occurred after one hour. Postmortem examination revealed diseased mitral valves with acute dilatation of the right heart and pulmonary edema. There was also definite sclerosis of the mouths of the coronary arteries and some arteriosclerotic areas in the abdominal aorta. Examination of the uterus failed to show any evidence of injury or hemorrhage due to the version and extraction.

The second patient, a twenty-one-year-old primipara, was first seen on admission to the hospital. There was a loud systolic murmur over the entire precordium, but the heart borders were within normal limits. She was approximately twenty weeks pregnant, had not missed any menstrual periods and had felt fetal motion two weeks before admission. She entered the hospital because of irregular uterine contractions. At this time her blood pressure and urine were normal, and there was slight pitting edema of both ankles. Two hours after hard labor began the membranes ruptured spontaneously and ethylene analgesia was commenced, but after a few whiffs of gas the patient became cyanotic so it was deemed inadvisable to give an anesthesia. Twenty-five minutes later the patient was delivered spontaneously of a two-pound fetus, and three minutes later the placenta was expelled spontaneously. The patient immediately became dyspneic and cyanotic, râles were present in the bases of both lungs, and she commenced to expectorate a frothy pink sputum. Her pulse rate jumped to 140 and in spite of repeated hypodermic injections of morphine and atropine, a venesection with the withdrawal of 200 c.c. of blood, and intravenous digalen, the patient succumbed in two hours. Postmortem examination was refused.

During the five-year period covered by this series, 7,670 patients were delivered at the Michael Reese Hospital with twenty-one maternal deaths, a mortality rate of 0.273 per cent. The mortality due to cardiac pathology, two deaths in 21 total, is 9.52 per cent. Hamilton and Kellogg[7] report a 1 per cent incidence of heart disease, but found that nearly 20 per cent of the maternal deaths were due to the cardiac condition. Carr and Hamilton[2] report a 6.4 per cent, Corwin[1] a 5.8 per cent, Daly[3] a 4 0 per cent and Scott and Henderson[15] a 2.33 per cent mortality rate from heart disease.

*Fetal Mortality.*—Of the 107 babies, three were delivered before viability. There were four fetal deaths (3.76 per cent) among the 104 which were viable. One was a macerated twin, one died of prematurity, one died during the spontaneous delivery of a primipara, and the fourth died during a version and extraction for a prolapsed cord following a bag induction for toxemia.

*Follow-up.*—Of the 100 patients who left the hospital, follow-up data have been obtained on 71. The follow-up period ranged from three months to over four years. All of the thirteen who were followed over four years were well and symptom-free. Of the eleven who were followed over three years, two had complaints referable to their cardiac pathology. Of the sixteen followed over two years, four had symptoms. Thirteen were followed one year; of these two had symptoms, the third patient is critically ill and will probably not survive.

Five were followed six to twelve months; one had symptoms. Of the eight followed three to six months none had symptoms. One, the patient with a coronary occlusion, had a third occlusion one month postpartum and died a week later of cardiac failure. The fifth patient in this group died three weeks after discharge from the hospital. This patient, the second who died in the follow-up group, had evidence of moderately severe decompensation during the latter half of her pregnancy and during labor.

It should be noted that only 11 (15.71 per cent) of these patients had symptoms or gave a history of cardiac embarrassment between the time of delivery and the follow-up. Forty patients have been followed over two years. The low mortality rate, 2.8 per cent, in this group is worthy of note.

## SUMMARY

The incidence of organic heart disease among the patients delivered at the Michael Reese Hospital during the last five years was 1.33 per cent; an additional 9.85 per cent had functional murmurs; 85 per cent of the cardiac patients had mitral disease of rheumatic origin. The remaining 16 per cent had myocardosis or congenital heart disease. In many women the cardiac pathology of rheumatic origin is stationary rather than progressive; such patients go through repeated pregnancies with no apparent additional disturbances to the circulatory system. Since the

length of labor in many cardiac patients is considerably shortened, and since many deliver prematurely a large percentage is able to tolerate spontaneous delivery; for the remainder the liberal use of morphine during the first stage is essential. In this latter group the second stage should be eliminated under ethylene anesthesia which is well tolerated by the cardiac patient. The frequency of toxemias of pregnancy is increased in women with organic heart disease. Sterilization should not be an indication for cesarean section. The mortality rate in this series was 1.8 per cent in labor, and 2.8 per cent in the delivered group which was followed. Only 15.71 per cent of the 71 patients followed up had symptoms or gave a history of cardiac embarrassment between the time of delivery and the follow-up. Forty patients in this group were followed over two years. A case report of coronary occlusion in pregnancy and labor is made.

## CONCLUSIONS

1. The conduct of labor in the cardiac patient must be individualized.
2. The cardiac pathology demands primary consideration; the pregnancy should always be secondary.
3. Radical obstetrics is unsafe in the presence of decompensation.
4. Neither organic heart disease, nor sterilization, nor the combination should be the indication for cesarean section.
5. The cardiac patient should enter labor well compensated.

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**Marmasse, J.: A Case of Spinal Anesthesia,** Bull. de la Soc. d'obst et de gynéc., p. 127, February, 1934.

The author reports a case where during labor spinal anesthesia was employed for a forceps delivery. One hour after delivery the anesthetic effects wore off and the patient complained of severe headache and nausea. One hour later she had a typical epileptic convulsion. In discussing such cases, the consensus of opinion at the French Surgical Congress in 1928 was that in cases of spinal anesthesia, meningeal irritation is the cause of loss of consciousness, epileptic convulsions, and psychic disturbances.

J. P. Greenhill.

# THE MANAGEMENT OF PREGNANT WOMEN WITH HEART DISEASE*

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FOR several years there has been endless controversy over the treatment of pregnant women who have associated cardiac disease. The controversial points have included diagnosis; the advisability of marriage and of pregnancy for such patients; the danger such patients encounter should they go through a pregnancy; the relative safety of delivery from below compared to delivery by cesarean section; the value of the sitting posture in delivery; the advisability of terminating pregnancy in the presence of cardiac failure and the effect of pregnancy upon the patient's life expectancy.

## MATERIAL

This paper is based upon a study of the women attending the Prenatal Clinic at Cook County Hospital. Until 1925 this hospital had no prenatal clinic, and the ward service devoted itself to caring for women who came to the hospital in labor or because of some one of the serious complications that require hospitalization during pregnancy. Up to this time our results in the treatment of pregnant women with heart disease was uniformly disappointing, probably because our experience in such cases was limited to those who came to the hospital with acute heart failure. The mortality in other clinics was far better than it was in ours but it was noted that every clinic with a low mortality for such cases had them under observation during pregnancy. In an effort to better our results, we organized a heart clinic for pregnant women. This was a part of the general heart clinic of the hospital in charge of Dr. Don Sutton, and to this special clinic we referred from our prenatal clinic every case in which there were symptoms or findings which might indicate cardiac disease. This practice was continued until the early part of 1933, at which time the clinic was becoming so large that it threatened to overtax our facilities. Since that time we have referred for study in the heart clinic only patients who showed definite evidence of heart disease. The special clinic still has under observation all of the cases which were referred to it except those who have been lost through refusal to cooperate.

During the time we have maintained this special clinic, 19,000 patients have been classified as new patients in the prenatal clinic. From this

*Read, by invitation, at a meeting of the Chicago Gynecological Society, May 18, 1934.

number 1,350 have been referred to the heart clinic. It appears, therefore, that one patient in fourteen presents something which might lead one to suspect an abnormal heart. Out of this group of 1,350, 126 have been selected as the basis of this report.

## DIAGNOSIS

These 126 cases comprise only those in which there is no reasonable doubt as to the presence of organic heart disease. The diagnosis of such disease, and the particular type of lesion present has been made or checked by the chief of the general Heart Clinic, Dr. Sutton.

From the original 1,350 cases sent to the cardiac group for study, the great majority have been eliminated for the purpose of this study. Among those which we have left for future investigation are tachycardias without other evidence of cardiac disease; those in which an associated hyperthyroidism might account for the cardiac findings; cases of dyspnea not definitely due to heart complications and arrhythmias without other evidence of heart disease. In short, every case in which the symptoms and findings were insufficient to substantiate the diagnosis of organic heart disease has been held for further study and is not considered in the present group.

We find, therefore, in our whole prenatal clinic, that the incidence of heart disease is 0.66 per cent. This is lower than the general incidence of heart disease, and lower than the incidence of heart disease in pregnancy in most clinics. Thus Munro Kerr[1] reports an incidence of 1.6 per cent in the Glasgow Maternity. Fitzgibbon[2] found 0.16 of 1 per cent of his cases at the Rotunda with a history of decompensation. Burton Hamilton[3] found that 1 per cent of his clinic patients had significant heart disturbance. Our low incidence may be partly due to the fact that for inclusion in this study we have insisted that incontrovertible evidence of organic disease be present.

## CLASSIFICATION

*The Mitral Group.*—Of the 126 cases, 107 had mitral disease and of these, 61 showed evidence of stenosis. In any group of cardiac patients mitral disease is the most common. Thus Pardee[4] reports 106 with 93 mitral cases, of which 64 showed evidence of stenosis. The age of the patients ranged from fourteen to forty-five. Forty-four came to us in their first pregnancy. Sixty-three had borne children previous to registration in our clinic, the parity running as high as twenty. Twenty-five were colored. Only two had positive Wassermann reactions. Eleven gave a history of previous heart failure. Thirty-seven patients have been under observation for more than five years.

In spite of the fact that this type of lesion falls under the general classification of rheumatic heart disease, only twenty-six gave a history

of rheumatism. Eight had repeated sore throats and two had chorea. Fourteen had scarlet fever. In other words, less than one-third gave a history of any type of rheumatic infection not including scarlet fever. This is a much lower incidence of rheumatic history than that usually recorded. McElroy[6] reports 200 cases from the Royal Free Hospital of London and finds 32 per cent with a definite history of rheumatism or rheumatic fever, and a total of 68 per cent with a history of some type of rheumatic infection. It is possible that the rather low level of intelligence of this group of patients may result in histories that are not accurate.

*The Aortic Group.*—There were twelve cases of aortic disease. Eight patients were twenty years of age or younger. Nine were colored, and five of these had positive Wassermann reactions. Three were diagnosed syphilitic aortitis and in two of these cases we were unable to make a diagnosis on first examination. Two patients gave a history of rheumatism. Half of the group came under observation in their first pregnancy. These twelve patients have been in the clinic for an average time of six years.

*The Combined Group.*—This group includes those in which there was definite evidence of both mitral and aortic lesions. There were seven such patients. All were Wassermann negative and their average time in the clinic has been six years. Only one was under twenty-one years of age, and she was the only one of this group we saw in her first pregnancy. One was colored. Six gave a definite history of rheumatism or rheumatic fever.

## SYMPTOMS

The most common symptom was dyspnea on exertion. In a group of patients such as ours this may be a very misleading indicator of the seriousness of the heart condition. Dyspnea is complained of by many pregnant women who have perfectly normal hearts. On the other hand, many patients with badly damaged hearts have relatively little dyspnea, and this is especially true of young individuals.

In the mitral group twenty-eight had intermittent dyspnea; twenty-four had moderate dyspnea and in only two was the dyspnea severe. Of the twelve aortic hearts only one had dyspnea as a complaint, but in five of the seven combined lesions it was rather severe.

Edema was the next symptom so far as frequency goes, but again this is a rather common finding in late pregnancy, and does not necessarily indicate myocardial strain. It was noted in twenty-one of the mitral cases, one of the aortics, but in none of the combined lesions.

Chronic cough was present in nineteen of the mitral group, three of the twelve aortics and four of the seven combined lesions. Chest pain occurred in twelve who had mitral, one who had aortic and three who had combined lesions.

Other cardiac symptoms were found in lesser degree, but a remarkable thing is that in a group of 126 badly damaged hearts thirty-five had no symptoms at all. If to this group be added those whose only symptom was mild intermittent dyspnea, 76 or 60 per cent of the whole series were without symptoms.

*Effort.*—We have not classified these patients according to the rules of the American Heart Association for two reasons. The first is that it is the greatest rarity to find an early pregnancy which falls in their Group III, that is cases which have symptoms or signs of heart failure when at rest. The second is that in our treatment we considered them only in relation to their ability to accomplish ordinary tasks. Thus we divided these patients into two classes:

1. Those in whom exertion is not more limited than in other pregnancies of the same duration.
2. Those whose exertion is definitely more limited than the pregnancy could account for.

The statistics relative to symptoms and effort ability refer to findings on first examination. Those cases in which symptoms developed later in pregnancy, or in which symptoms became aggravated will be referred to in considering the management of these patients.

## MANAGEMENT

Previous to the organization of this clinic, a considerable number of patients with definite evidence of heart failure were sent to the wards in labor. During the time the cardiac clinic for pregnant women has been conducted, a certain number of patients who had not attended the clinic were sent in under similar circumstances. Our inability to care for these patients successfully was very striking. Even those patients not in labor but with advanced heart failure while pregnant resulted in a high percentage of fatalities. Our general plan therefore was to prevent these pregnant cardiacs from developing heart failure. Pardee[4] suggests that "the best treatment of severe cardiac failure is prevention, and this means keeping watch during pregnancy for the appearance of increasing cardiac difficulty, appropriate treatment of the heart as soon as this is discovered and the interruption of pregnancy if the heart fails to respond after two or three weeks." Our previous experience led us to subscribe to this suggestion without reservation, so that we devoted ourselves to prevention rather than treatment.

It became necessary to arrive at some sort of a standard that would enable us to know when these patients began to lose their cardiac reserve or show signs of beginning heart failure. At first we used the exercise test, suggested by Pardee[4] but later we substituted a simpler test, and one that has been quite satisfactory. These patients were all examined at frequent intervals during their pregnancies. So long as they were

able to carry on their ordinary activities without distress, we considered them in no danger. Whenever a patient was unable to do ordinary light housework without dyspnea, or without fatigue; whenever she had difficulty in lying down without more than one pillow under her head; whenever she developed a cough even with no other symptoms, we considered that her myocardium was laboring under strain and she was immediately hospitalized. We were cognizant of the generally accepted physiologic changes of the heart in pregnancy, but in these patients all of whom had damaged hearts, we believed that anything which gave evidence of myocardial distress was sufficient to call for hospitalization. If at routine examination the pulse was over 100 when at rest, or if any irregularity developed, she was hospitalized even if symptoms were absent.

In order to protect the patients from the development of such conditions they were required to spend two hours of each day at complete rest. No other form of treatment was carried out at home. Digitalis was never given during pregnancy while the patient was at home. If in spite of this rest period the patient could not accomplish ordinary household tasks without evidence of cardiac strain she was hospitalized at once.

In the hospital she was treated symptomatically, and whenever the symptoms were of great importance the advice of the physician in charge of the heart clinic was requested. Such a patient was kept in the ward so long as it seemed wise; whenever she could be up and about without distress she was released. Even in the hospital we depended much more on rest, even though secured by sedatives, than on cardiac drugs.

It was our intention always to hospitalize these patients for a few days before they went into labor unless we were convinced of their ability to remain at home safely until labor began. Thus all of the patients with combined lesions were hospitalized before labor, the period of hospitalization ranging from three to twenty-four days. Of the aortic group 40 per cent were hospitalized before labor, and 30 per cent of the mitral group. In addition to this, twenty-four patients were hospitalized at some other time during pregnancy and some of them several times. One para viii was in the hospital for a total of twelve weeks before labor began. She gave a history of heart failure on four previous occasions, and objected to either abortion or sterilization, so that after the fourth month she spent most of her time in the hospital. She was one of the few patients in whom digitalis was necessary over protracted periods.

By this method of hospitalization at the first sign of significant evidence of myocardial stress we were enabled to carry the entire group through pregnancy without the development of alarming symptoms. Two factors undoubtedly contributed to this gratifying result. One was an

efficient social service worker who saw to it that patients returned to the clinic as frequently as we cared to see them. The other was the fact that hospitalization was without cost to the patient so that we were able to send them to the ward whenever and as often as we deemed advisable without considering their financial condition.

Our treatment during labor was likewise extremely simple. Prenatal examination enabled us to make very accurate prediction concerning the presence of cephalopelvic disproportion. Once this factor was eliminated we had to consider only the ability of the heart to withstand the strain of labor. It had been noted by many observers, e.g., Daly,[5] Pardee,[4] Breed and White,[7] Herrick,[8] Corwin et al.,[9] Hay,[10] that cardiacs who begin labor without evidence of heart failure do very well. Inasmuch as our entire group were without marked cardiac distress at the beginning of labor, we felt that uncomplicated labor presented no great hazard. In labor, as well as during pregnancy, no distinction was made between the various types of heart lesion other than as a matter of record. We were interested at all times in the heart's functional ability rather than in its anatomic defects.

Most observers have noted that the first stage of labor, being principally a smooth muscle activity, puts no great strain on the myocardium except that resultant from exhaustion or from mental unrest. Both of these we tried to prevent by sedation. The routine sedative used was morphine gr. $\frac{1}{4}$ and scopolamine gr. $\frac{1}{150}$ hypodermically. This was given in primigravidas as soon as the cervix was dilated 3 cm., and in multigravidas as soon as labor definitely had begun. The dose was repeated after four hours if it seemed advisable. In the second stage if progress was rapid, the normal process was not interfered with. If at any time after the cervix was completely dilated progress was slowed or there developed any symptoms of cardiac distress, delivery was accomplished by forceps under ether. It was our experience that these patients when once in labor made satisfactory and frequently very rapid progress.

*Length of Labor.*—In the primigravidas the longest labor was twenty-nine hours, and it was this patient who showed moderate cardiac collapse early in the second stage. The shortest labor was six hours and the average was ten hours and fifty minutes. Those who had borne children previously had an average labor of five hours and forty minutes, the extremes being three hours ten minutes and eight hours fifty minutes.

## RESULTS

Under this management 126 patients have delivered 189 babies. Two cases aborted spontaneously before five months. Three nonviable premature babies, including one pair of twins, were born. Eleven went

into labor prematurely but after their babies had become viable. Two of these babies failed to survive. One full-term normally delivered infant developed pneumonia and died.

The operative procedures on mothers included one bag induction for associated hypertension and preeclamptic symptoms; one bag induction because the pregnancy was at term. This procedure was not recommended by anyone connected with the antenatal cardiac group. One cesarean section in a multipara done to permit sterilization; 23 low forceps and five midforceps were done in 51 primigravidas; one low forceps and three midforceps were done in 79 multigravidas, and one version and extraction was done on the second twin of a gravida iii. Ether was used in all operative deliveries.

*Maternal Results.*—No patient died during pregnancy or labor. Two patients, one primigravida and one gravida ii showed evidence of acute failure during labor. The gravida ii had been in the ward for several days before labor began because of the gravity of her cardiac condition. Through some error in technic, no one was made aware of the patient's labor pains until the cervix was completely dilated, and there was no first stage analgesia. The patient was rushed to the delivery room, where she at once developed the classical signs of acute heart failure and was delivered ten minutes later in the sitting position. This was the only patient delivered in this position. The primigravida came to the hospital in labor, having refused to accept our advice of hospitalization a week earlier. At the end of a long first stage she showed evidence of moderate cardiac distress, and was delivered by forceps. Both mothers survived. Both babies were born alive, but the baby of the gravida ii died of pneumonia on the seventh day.

One patient died before leaving the hospital. This was a gravida ii whom we had delivered successfully of her first baby two years previously. She was in the ward for observation before labor, and had had no trouble of any sort during pregnancy. At term a bag was inserted to induce labor. No other indication was present for the induction, and it was not recommended by anyone connected with this study. The bag was removed after twenty-four hours and labor started ten hours later. It was an easy four-hour normal labor. On the fifth postpartum day the patient started to run a temperature, which persisted, and gradually increased, until death occurred in the sixth postpartum week. At no time was there definite evidence of pelvic infection, and a diagnosis of malignant endocarditis was made. This was confirmed at autopsy, when most extensive endocardial growths were found, but no other evidence of focal infection.

*Subsequent Results.*—One of these 126 patients died after she left the hospital. This patient was forty-five years old and came to us in her twentieth pregnancy. Six weeks after she left the hospital, she returned in complete cardiac collapse. In ten days she was discharged recovered. Nevertheless she returned at frequent intervals and died on her fifth hospitalization, nine months after delivery. This was not an unexpected death, for most observers agree that the life expectancy of a severely damaged heart is about forty-five years. Reid[11] says, "I feel safe in concluding that as far as these statistics have value they support my clinical impression that women with rheumatic heart disease die before their time not because of marriage and pregnancy but on account of the natural evolution of this disease."

Except for this one case none of these patients was unable to return to the heart clinic for the routine examination which we made six weeks after discharge from the hospital.

Twelve patients have returned to the hospital after delivery because of heart failure. Except for the fatal case just noted, no one returned before five months. These patients have been in the hospital or in a convalescent home from one to five times. Their average age is twenty-eight years. Three have had only one pregnancy. Four have gone on for nine to eighteen months with chronic auricular fibrillation and greatly enlarged livers. One is a para vi now forty-one years old; one a para viii, thirty-six years old; one a para iii, thirty-one years old; and one a para i, twenty-one years old. This we expect, and we expect it to increase. Cohn[12] notes that the annual death rate for rheumatic hearts between twenty and forty years of age is about 3.5 per cent.

Besides the one patient sterilized at cesarean section, ten have been sterilized later, all multiparas. One was sterilized by x-ray. Although she had gone through her three pregnancies with us, and in spite of the fact that we had her in the operating room three times, at no time was her heart in such condition that we felt justified in attempting operative procedures. It is not our attitude that repeated pregnancies result in no increase in heart damage. Neither are we willing to say that the life expectancy of these patients is not diminished by repeated pregnancies. Therefore, we believe that any one of these patients should be sterilized whenever she requests it, and each patient is so informed. The indigent, however, are frequently mentally indolent as well so that while they are not pregnant they do not consider sterilization, and they usually report when the next pregnancy is so well advanced that we consider sterilization only on the most marked indications.

*Comparative Results.*—During the time that this group was under observation, 79 patients with cardiac diseases in pregnancy came to the hospital for treatment or for delivery. All of these came direct to the hospital with congestive heart failure; none of them had attended any clinic previously. Sixty-one were in labor. Twenty-one were in their first pregnancy, 54 were at or near term. Twenty-one of these patients died. Five died undelivered. The others died from ten hours to eleven days after delivery.

No attempt is made to compare the seriousness of the cases which had no prenatal care with those which we had in the clinic. These are cited only to show the value of preventing heart failure. Carr and Hamilton[13] in an excellent report of 500 cases had a very low mortality in the patients who were under control during pregnancy. They also note that in private practice "there have been no deaths so far among the patients that have been under strict medico-obstetric control from early in pregnancy or before pregnancy, if one excepts two patients who died undelivered of diffuse bronchopneumonia. It is equally true that for cases not under strict control the death rate is high."

## SUMMARY

A series of 126 women with severely damaged hearts has been under observation and strict control during 192 pregnancies.

No patient died during pregnancy or labor.

One died six weeks postpartum from an acute bacterial endocarditis which developed after labor.

One died nine months postpartum at the age of forty-five.

No patient was delivered by cesarean section because of the heart condition.

The most important factor in the care of these patients is the prevention of heart failure. In this effort the cooperation of an internist

and an obstetrician, both of whom have had wide experience in observation of these patients, is invaluable. When heart failure is prevented during pregnancy, disaster during labor or in the postpartum period is a very rare occurrence. It has been our experience that in the absence of obstetric complications necessitating other procedures, delivery *per vaginam* produces results that are extremely gratifying.

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## DISCUSSION

(Papers of Drs. J. E. Fitzgerald, Ralph A. Reis and L. E. Frankenthal)

DR. LOUIS N. KATZ.—As pregnancy is a normal process for many if not all women, it can only be viewed as a complication of heart disease. Pregnancy and labor are no different from any other type of work imposed upon the cardiac patient. This is the point of view which should be followed by obstetricians and cardiologists.

The blood volume and basal metabolism are increased in pregnancy, particularly in the last months. These changes put an additional demand on the heart. Measurements have shown that vital capacity is decreased in pregnancy, particularly in the last few months. These pulmonary alterations further burden the heart.

There is a real need to examine all patients early in pregnancy when the burden of pregnancy on the heart is not great. I wish to emphasize that there may be difficulty in diagnosing heart disease because many of the clinically accepted signs of heart disease may occur late in pregnancy in the absence of organic heart disease.

One sign of heart failure the clinician often overlooks is the presence of râles in the base of the lungs which is a reliable sign of congestive heart failure.

A patient should be advised against pregnancy, if she has had a recent attack of acute rheumatic fever, if her exercise tolerance is low, if her heart is enlarged or if she has auricular fibrillation.

If the pregnant patient develops symptoms and signs of heart failure in the first three months of pregnancy it is wise to terminate the pregnancy. If heart failure comes on later, it is best to let the patient go on to term.

Labor should be made as easy as possible for the patient. There should be many rest periods during the first stage. In the second stage it would seem that all the assistance that is at all compatible with good practice should be given. After the placenta is expressed, the old-fashioned idea of binding the abdomen is of real value. If the patient has congestive heart failure, it would be better to keep her in a semisupine position throughout labor.

DR. DON C. SUTTON.—I wish to endorse the liberal use of morphine during the first and second stages of labor.

The course of rheumatic heart disease, with some well-known variations, is definite; some patients die of the initial endocarditis; others of severe cardiac

damage at an early age; in many the process becomes quiescent for a period of years, but as a rule, some time between the ages of thirty and forty-five, they succumb.

When the findings of heart disease are so indefinite that a positive diagnosis cannot be made, then the severity of the involvement is so slight that it makes no difference whether or not it is called a normal heart.

The obstetrician deals almost entirely with rheumatic heart disease, and as more than 80 per cent of this group have involvement of the mitral valve, of course most of the cases dealt with are mitral disease, and therefore the most serious.

The girl who has rheumatic heart disease which is not decompensated has the right to marry and perform her main duty of life, the bearing of one or two children, with little worry about materially marring her future if she receives proper prenatal care.

DR. JAMES G. CARR.—My contribution is to present a summary of 23 cases from the records of the Evanston Hospital during the past ten years. Mitral disease was present in eighteen, twice combined with aortic involvement. In three instances the cardiac disease was apparently only a tachycardia in individuals who had formerly had a thyrotoxicosis. One patient sustained a coronary occlusion during her fourth pregnancy; another was regarded as having a dilated heart, for which she was given digitalis during a good part of her pregnancy. In three patients therapeutic abortion was performed early in the pregnancy. In four instances premature labor was induced. Five patients were delivered spontaneously, three of them at term, one at seven and a half months, and another, a para ii, at eight months. Four patients, late primiparas, were delivered with low forceps at term.

Seven patients were subjected to cesarean section. One was in the hospital under observation for six weeks prior to term. A second patient was confined to bed for most of the time prior to the cesarean section. She stood the operation badly and for two or three days was seriously ill. A third patient was subjected to section near term in her second pregnancy, after having gone through a severe collapse at the time of her first labor. Another patient, a woman of thirty-four, was in bed most of the last trimester because of dyspnea and edema when she attempted to be up and around. The cesarean sections were attended with no operative mortality, but one patient who was operated upon at term died within a few weeks of subacute bacterial endocarditis. This patient entered the hospital with fever.

One of the five patients delivered spontaneously was admitted in labor two or three weeks prior to term and easily delivered within a very short time. Her admission temperature was 100°+. She had a pronounced collapse, with marked cyanosis and tachycardia, so marked that she was kept in an oxygen tent for many days. Within a few days, positive cultures confirmed the diagnosis of subacute bacterial endocarditis, from which she died six or eight weeks after delivery.

The patient who continues through pregnancy to be free from signs of decompensation may be safely trusted to go into labor. But the patient who shows signs of decompensation should not be allowed to enter or go through labor.

Heart disease is not a statistical problem. It is necessary for the obstetrician and internist together to decide whether a woman, upon the basis of her response to the usual and necessary demands of living during the last months, is able to enter upon the delivery of her baby in a normal way. It is a question of judgment which must be based on experience. No dogmatic rule is acceptable as the basis of our decision as to treatment.

DR. HAROLD H. HILL.—Dr. L. Feldman and I made a study of the electrocardiographic tracings of normal hearts in pregnancy at the University of Illinois. We made the first tracing between the thirty-second and thirty-sixth week, the second

about eight days postpartum and a third at the six weeks' postnatal examination. The third tracing was soon abandoned as there was little or no difference from that of the second reading. Thirty-six women were selected in all. Twenty-one or 58 per cent showed various degrees of left axis deviation, ranging from 13 degrees to 80 degrees rotation in a counterclockwise direction. Variations of under 13 degrees rotation of the electrical axis were not considered significant.

The findings are in accord with the belief that late in pregnancy the heart is in practically a transverse position due to a rising diaphragm and not necessarily to hypertrophy.

DR. WILLIAM C. DANFORTH.—In the first trimester moist râles at the base of the lung associated with other signs of decompensation cause severe anxiety. I have always felt that decompensation in the first trimester calls for termination of the pregnancy. The mere presence of a murmur itself is of very little importance. Men may do severe physical labor with cardiac lesions. The essential thing is whether the heart is doing its work and can continue to do it.

I feel that the majority of women should be delivered vaginally. Where abdominal delivery is used the old classical section should not be performed. It is the poorest way of delivering a patient with cardiac disease, because stormy convalescence may subject the heart to much strain.

The use of morphine during the first stage is important. The length of the first stage is of secondary importance. Of primary importance is that the woman should not be allowed to fatigue herself and should obtain sufficient rest.

Occasionally we hear the recommendation that pregnancy should be terminated prior to term so as to have a smaller baby and an easy labor. This is unwise. It is wiser to allow labor to come on normally because the labor itself is more normal.

I am not as enthusiastic about the use of high forceps as is Dr. Katz, perhaps because I have been on the obstetric firing line.

As far as anesthesia is concerned, I have felt strongly that ether should be used.

With the cooperation of the obstetrician and internist the majority of these patients can be carried through safely, and operative delivery is indicated only in a selected small minority.

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**Klaften, E.: A Contribution to the Clinical Aspects of Disgerminoma Ovarii,** Zentralbl. f. Gynäk. **57:** 736, 1933.

The solid, large cell carcinoma of the ovary, named "Disgerminoma" by Robert Meyer, contains large, round or polyhedral epithelial elements whose protoplasm appears grossly vacuolated. The connective tissue shows hyaline degeneration, and the tumors are richly infiltrated with lymphocytes and many mitotic figures appear. They are rich in cell glycogen, have no hormonal influence on the sex apparatus or the sex function, and appear characteristically in young individuals. As they develop from undifferentiated germ cells they may occur in either sex.

They are associated with 3 types of individuals: (1) pseudohermaphrodites (27 cases have been reported in pseudohermaphrodites); (2) individuals with hypoplastic constitution; (3) normal individuals with a somewhat lowered sex function, i.e. late menarche, frequent sterility.

They are quite malignant and the prognosis is not good, though some excellent results have been reported.

WILLIAM F. MENGERT.

# HEART DISEASE COMPLICATING PREGNANCY

## A Clinical Study*

William Schuman, M.D., Baltimore, Md.
*(From the Obstetrical Service of the Sinai Hospital)*

IN THE Obstetric Clinic of the Sinai Hospital, a member of the medical staff, Dr. B. J. Cohen, recently was placed in charge of the cardiac patients, studying them in the prenatal clinic and in the ward, intra- and postpartum, with a view to obtaining accurate data on this important medical problem. The series to be discussed in this paper consists of those cases studied prior to his connection with the clinic, with the exception of a few that have come under his observation. The majority of this group received a fairly complete cardiac work-up, having been referred to the cardiac clinic as soon as the cardiopathy was recognized, and were followed by one of two or three cardiologists until the termination of pregnancy, and again after discharge from the hospital. Every case has been carefully followed, and represents the closest cooperation between the cardiac, obstetric, and social service departments, the latter an invaluable cog in the study and treatment of the cardiopath.

The series of cases about to be presented, however small, represents a pretty good cross-section of cardiac clinical material. In all, there are 25 cases of heart disease found at some period of pregnancy or shortly postpartum. They are all ward cases, and therefore do not constitute all the heart cases admitted to the obstetric floors of the Sinai Hospital. The data on private cases being less complete with regard to prenatal histories, it was thought best to eliminate them. However, it can be said with a fair degree of accuracy that the incidence of heart disease among private obstetric patients is considerably less than among the ward cases and, if studied, would prove only half as numerous, a fact which emphasizes the rôle of environmental conditions as an etiologic factor in cardiac disease.

Of the 25 cases, 21 occurred between Jan. 1, 1930 and Nov. 30, 1932, during which period 918 mothers were delivered on the ward service. This gives an *incidence* of one in every 44 cases, or 2.3 per cent. The 25 patients gave us the opportunity of studying 31 pregnancies. On the basis of the last pregnancy observed, 9 were primiparas, 8 were para ii, 2 were para iii, 1 was para iv, and 5 were more than para iv. Two of the women died as a result of their pregnancy, a maternal mortality of 8 per cent. A third woman died more than six months after delivery with subacute bacterial endocarditis. As far as we are able to determine,

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22 of the 25 patients are alive today. Only one viable child died (stillborn) out of 18 full-term deliveries. Another full-term child was removed at autopsy from the uterus of its mother who died undelivered.

Eleven individuals gave a definite rheumatic history. The same number had a previous cardiac history, that is, had been treated either in our dispensary or hospital, in some other institution, or by a physician prior to the pregnancy that came under our observation. Fourteen had no previous knowledge of a cardiac condition, and in three cases, cardiac disease was not recognized until labor or the puerperium. In studying the relation of rheumatic history to the severity of the disease, it was noted that of the eleven with positive history, 3 were mild cases, and 8 severe; and of the 14 with no rheumatic history or of doubtful etiology, 6 were mild, and 8 severe. In other words, the chances for a severe lesion are twice as great when the rheumatic history is definite.

The types of lesions as determined by physical signs show a preponderance of the double mitral lesion, 10 of the 25 cases having a mitral stenosis and insufficiency. Next in frequency came mitral stenosis with 5 cases, and third, mitral insufficiency with 5; aortic insufficiency and mitral stenosis accounted for another, combined aortic and mitral insufficiency for still another. One of the two cases that died was diagnosed postmortem as chronic endocarditis of the mitral and aortic valves with cardiac hypertrophy and chronic nephritis. It is interesting to note that 7 of the 10 cases with the double mitral lesion were severe cardiacs, that 4 of the 5 with mitral stenosis alone were severe, and that 3 of the 5 with mitral insufficiency were mild cases. The two cases in which the aortic valve was involved differed markedly in their clinical aspects, one never showed signs of decompensation and delivered spontaneously without embarrassment, the other showed signs of decompensation since early in pregnancy and was sterilized following cesarean section at term.

The plan of treatment in this series was based on the particular needs of each individual case, and not on a group classification similar to those of Pardee, Hamilton and Kellogg, and others. Of the 25 cases, 18 were delivered at term, 6 were interrupted, and 1 died undelivered. Six cesarean sections with sterilization were performed at term, four abdominal hysterotomies and sterilization were done before the viability of the child, and two inductions of abortion were carried out. Ten of the 25, therefore, were sterilized.

Let us consider in some detail the cases treated by cesarean section. There were 6 cases, of which 4 were primiparas and 2 para ii. Four had a definite rheumatic history, 1 indefinite, and 1 negative. They all could be classed as severe cardiacs. Three had combined mitral stenosis and insufficiency, 2 had mitral stenosis, and 1 had aortic insufficiency. Preoperative preparation consisted in absolute rest in bed in hospital for from three to fifty days, and in some cases digitalization. One patient received Lugol's solution. All cases had the classical operation. Anesthesias used were: ether in three cases, local followed by ether in one case, avertin supplemented by local and ether in one case, and spinal anesthesia in one case. The condition of the patient during operation was good in five cases. One patient, who started under local infiltration, went into acute fibrillation at the very onset of the operation, and was finished under ether. Her collapse was ascribed by some to the introduction of novocaine (and adrenalin) into the circulation. The condition immediately following operation was good in four cases, and the patient just described rallied and was in satisfactory condition at the end of the operation. In another case, the pulse rose from 70 to 130 following section. She subsequently died on the seventh day postoperative, and is the only patient in the series that died following delivery. The postoperative complications were: distention and gastric dilatation followed by auricular fibrillation in the woman who died, one pulmonary infarction or pneumonitis which cleared up in three days, and one pelvic infection. The others had a smooth convalescence, and

showed no more discomfort or tachycardia than the usual case of cesarean section. The number of days spent in hospital following operation was from nineteen to twenty-six. There was no fetal mortality in this group.

Considering the group of four cases in which pregnancy was interrupted by abdominal hysterotomy and sterilization, we again note the preponderance of the combined mitral lesion. Three had mitral stenosis and insufficiency, one had mitral stenosis and a possible aortic insufficiency. Periods of gestation were two, two, three, and five months. Three of the four had a positive rheumatic history. All were operated upon under ether anesthesia, and in three the condition during operation and immediately postoperative was good. One patient had a temporary collapse, but quickly rallied.

Induction of abortion was performed in two cases. In the one, the duration of pregnancy was three and one-half months. The cervix was packed with gauze under twilight sleep. She also had a definite rheumatic history, and had a double mitral lesion. She had a moderate tachycardia for eight days postoperative, but subsequently ran a normal course. The second case interrupted was a woman thirty-seven years of age, who had 2 living children and 3 therapeutic abortions. She has had auricular fibrillation for eight years without definite etiology, and with no demonstrable murmur. She was curetted at two months under local infiltration without event.

## HEART DISEASE AND PUERPERAL MORTALITY

In going over the general maternal mortality in the Sinai Hospital, it was found that heart disease was second among the causes of death in pregnant women. Eclampsia ranks first. Out of a total of 19 obstetric deaths (ward and private) from all causes, 4, or 21 per cent (corrected: 3, or 16 per cent), were attributed to heart disease.

If the figures 10, 15.8, and 16 per cent for heart disease in puerperal deaths found in Reid's, Greenhill's, and my series, respectively, were generally true, this complication of pregnancy would take its place among the leading causes of maternal mortality. The discrepancies between hospital reports and general statistics can only be explained by the fact that the latter include all sources of information, deliveries by midwives and incompetent physicians, as well as unattended cases, among which, I am sure, are countless cases of unrecognized heart disease. DeLee, in his textbook, states that "heart disease in labor is often overlooked." Likewise, I am of the opinion that heart disease in pregnancy exacts a much greater toll of life than is generally believed.

## CONCLUSIONS

There are several important lessons to be learned from an analysis of this series. First, it makes one more cardiac conscious. Second, it stresses the importance of a careful history from the point of view of etiology of heart disease, especially the rheumatic factor. Third, it emphasizes the necessity of careful auscultation of the heart, for it has been demonstrated unmistakably that mitral stenosis and a combined lesion constitute the most severe types complicating pregnancy.

Most obstetricians confess their inability to time and diagnose accurately heart murmurs. That is excusable, but for an obstetrician or physician to fail to interpret clear facts in the history or to evaluate improperly the symptoms of beginning decompensation is unpardonable.

While the classification by Pardee and others is of great assistance in the study of cases, I am of the opinion that a more simple division into mild and severe cases would be more satisfactory and less difficult. I believe it can be safely said that a mild cardiac can be treated as any other obstetric patient, with the following reservations, limitation of exercise, especially in anticipation of confinement, and shortening of the second stage of labor. The severe cardiac, however, is a problem that must be treated individually. "The decision (whether or not to interrupt pregnancy in any given case) calls for knowledge, large clinical experience, and good judgment." (E. P. Davis.) The parity of the patient, the period of gestation at which she is first seen, her ability to obey instructions, her religion, desire for children, the question of sterilization, and the presence of other complications must all be taken into consideration. If a woman is seen in the early months of pregnancy and has already decompensated, abdominal hysterotomy and sterilization after return of compensation is the treatment of choice. If a patient is seen for the first time after the period of viability with

TABLE I. INCIDENCE

| YEAR | DELIVERIES | CARDIACS | INCIDENCE |
|---|---|---|---|
| 1930 | 298 | 6 | 1:50 |
| 1931 | 286 | 5 | 1:57 |
| 1932 (11 mo.) | 334 | 10 | 1:33 |
| | 918 | 21 | 1:43.7 |
| | | | Per cent 2.3 |

TABLE II. RELATION OF HISTORY TO SEVERITY OF HEART DISEASE

| | TOTAL | MILD | SEVERE |
|---|---|---|---|
| Pos. rheumatic history | 11 | 3 | 8 |
| Neg. rheumatic history | 14 | 6 | 8 |
| | 25 | 9 | 16 |

TABLE III. TYPE OF LESION AND RELATION TO SEVERITY

| | TOTAL | MILD | SEVERE |
|---|---|---|---|
| Mitral stenosis and insufficiency | 10* | 3 | 7 |
| Mitral stenosis | 5 | 1 | 4 |
| Mitral insufficiency | 5 | 3 | 2 |
| Aortic insufficiency and mitral stenosis | 1 | 1 | 0 |
| Aortic insufficiency and mitral insufficiency | 1 | 0 | 1 |
| Doubtful | 1 | 1 | 0 |
| Cardiac failure: aortic and mitral lesions, chronic nephritis (autopsy) | 1* | 0 | 1 |
| Auricular fibrillation | 1 | | 1? |
| | 25 | 9 | 16 |

*One died.

TABLE IV. TREATMENT (DELIVERY)

| | CASES | DEATHS |
|---|---|---|
| Spontaneous or low forceps | 11 | 0 |
| Version and breech extraction | 1 | 0 |
| Cesarean section and sterilization | 6 | 1 |
| Abdominal hysterotomy and sterilization | 4 | 0 |
| Induced abortion | 2 | 0 |
| Undelivered | 1 | 1 |
| | 25 | 2 |

TABLE V. MORTALITY

| | |
|---|---|
| Maternal, 2 out of 25 (Usual 8 or 10 per cent) | 8.0 per cent |
| Fetal (corrected), 1 out of 18 delivered viable babies | 5.5 per cent |

TABLE VI. HEART DISEASE AND MISCELLANEOUS MATERNAL DEATHS

| | | | |
|---|---|---|---|
| Total obstetric deaths | 19 | | |
| Due to heart disease | 4 | | |
| Percentage | 21.0 | Corrected | 16.0 |

a decompensated heart, absolute rest until return of compensation followed by cesarean section and sterilization under ether or local anesthesia gives the best prognosis for mother and child.

Another lesson to be learned from a study of this kind is that the danger is not over with the end of labor. The puerperium may be the most treacherous period, cardiac failure often setting in early or later in the postpartum. This occurred in two of our cases, in both of which heart disease was unrecognized before labor. Both these cases might have been diagnosed antepartum had a second examination of the heart been made in the last prenatal visit. I have adopted and recommend the practice, whenever making a final obstetric examination for the detection of disproportion or malpresentation, also to take an extra minute to examine the heart and base of the lungs; in short, a repetition of the physical examination at term.

## COMMENT

The management of the cardiac in pregnancy is an acid test of her attending physician. While the internist or cardiologist consulted in a given case assumes part of the burden, the ultimate responsibility is the obstetrician's. "In no class of cases is the benefit of intelligent prenatal care and medical observation more strikingly shown than with these patients, and, on the contrary, the absence of this care greatly increases the morbidity and mortality in the presence of this complication." (E. P. Davis.) No better example of unintelligent care is that of a cardiac patient who walked several miles the same day she fell into labor, because, as she said, "the doctor told me to walk every day in the fresh air." Hamilton and Kellogg state that delivery of a patient

in heart failure should be regarded as an indication that some one has blundered. Certainly, Medicine exacts of one of her calling a difficult assignment in the treatment of the pregnant cardiopath.

From the point of view of prophylaxis, we must begin in early life. The adolescent is particularly susceptible to the rheumatic virus, and her health should be carefully supervised, in an effort to prevent rheumatic fever, chorea, tonsillitis, and their complications. The prevention of rheumatic disease by tonsillectomy is quite a debatable question; nevertheless, I would urge the operation routinely in very young children. Better hygiene among the poor is necessary before a reduction in heart disease may be expected. (In one family, two sisters had rheumatic heart disease for which one was sterilized, and a younger sister had Saint Vitus's dance.) The question of marriage in the presence of a cardiac lesion is a subject in itself and need not be discussed here. When one considers the numerous specialists concerned from the beginning to the end of this great problem, the pediatrician, the hygienist, the general practitioner, the internist, the cardiologist, the anesthetist, and the obstetrician, one begins to realize its tremendous scope. It is only by the perfect cooperation between these various branches and by careful research into every aspect of this problem, that we can hope to reduce the great toll of lives sacrificed on the altar of motherhood by reason of a diseased heart.

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## DISCUSSION

DR. B. J. COHEN.—It is very important that the obstetrician should be cardiac conscious, should take a careful history, and should auscultate thoroughly. Then if the patient should have the slightest anomaly, such as accentuated or roughened sounds, etc., she should be immediately referred to the attending internist or cardiologist. Emphasis should be made on the following important points:

1. *History.*—Patients with a definite history of tonsillitis, chorea or acute rheumatic fever are followed as cardiacs, irrespective of the subjective symptoms.

2. *Anemia.*—Routine blood counts should be done to determine whether or not patient has anemia. One case of mitral stenosis after delivery developed fever. This case was not in our series and was referred for a diagnosis. The patient had a very classical case of subacute bacterial endocarditis, with anemia, splenomegaly,

*Streptococcus viridans* septicemia, etc. Of course death occurred in a few months after delivery. I do feel that this complication may have been prevented, if the patient had been under observation earlier, and pregnancy had been terminated.

3. *Diagnosis and Classification Into Groups.*—I do not feel that a complicated grouping of the cardiac cases is accurate or consistent with the method of treatment. I have formulated a very simple classification. The first group is the so-called undiagnosed or deferred types, which includes cases showing one or more than one of the following findings: (a) slight cardiac enlargement, (b) snapping or roughened or split mitral sounds, (c) accentuated second pulmonic sounds, (d) extra systolic arrhythmia or questionable systolic murmurs with or without subjective symptoms.

The second group comprises all cardiacs in which a definite diagnosis has been made of valvular cardiac disease. It is amazing how frequently we see sudden onset of decompensation with dyspnea, palpitation and tachycardia occur in mitral stenosis cases without any warning, and yet clinically the patient would be regarded as having very good myocardium from routine examination. We therefore regard all valvular cases as severe ones, to be observed closely, so that proper treatment and rest can be instituted at the proper time.

X-rays of heart and electrocardiograms are taken at different intervals throughout the pregnancy. The usefulness of the latter procedure as an aid to diagnosis is still uncertain.

It is important to remember that there are *no* signs that enable me to diagnose a very early failure, and this alone is a warning to prevent pregnancy whenever possible in a cardiopath, not only to lessen the immediate mortality rate, but also to preserve the myocardium of the patient for the future.

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**Moench, G. L.: Variations of the Solubility of the Cervical Mucus in Relation to the Menstrual Cycle**, J. Lab. & Clin. Med. **19**: 358, 1934.

Moench, in the course of examining sterile couples, has repeated Kurzrock's experiments, using mainly the gross method of immersing the cervical mucus in the semen. Infected cervical mucus was practically not digested by semen (in agreement with Kurzrock) but microscopically was observed penetration of the spermatozoa into the mucus. The degree of penetration seemed to depend on the viscosity of the mucopus or mucus, rather than upon any lytic action of the semen.

Moench favors the idea that the solubility of the cervical mucus varies at different times of the menstrual cycle. It is known that follicular fluid and also the normal secretion of the fallopian tubes and the uterine body dissolve the cervical mucus. In fact, the rubbery consistency of the cervical plug during pregnancy has been explained as being due to the absence of the solvent action of the combined tubouterine secretions. It may be that there is a direct action of the ovary through the folliculin in the blood stream on the cervical mucus, although determinations of circulating female sex hormone were not made, and without such determinations no definite conclusions can be drawn. The few cases presented seem to point to a variation in the properties of the cervical mucus, dependent apparently on ovarian activity.

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# EMBRYONAL CARCINOMA OF THE OVARY (DISGERMINOMA)*

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EMBRYONAL carcinoma designates a malignant epithelial tumor whose constituent cells present the morphology found in the early developmental stages of the organ in which the growth originates. Both male and female gonads present an embryonal carcinoma with identical gross and microscopic appearance. This surprising occurrence is explained by the following factors:

1. In the first month of asexual embryonal growth, the primitive genital ridge contains sexual and germinal cells.

2. The same sexual and germinal cells comprise the building stones of the ovary and testicle which begin their differentiation between the fourth and sixth weeks of development. In this complex embryologic metamorphosis some of these undifferentiated embryonal cells may be displaced to undergo later neoplastic growth.

3. Arrested gonadal development occurs in both sexes as seen in cryptorchidism and hermaphroditism. It is associated with retention of immature cell types.

4. Both ovary and testicle contain omnipotent sex cells from which teratomas with their irregular admixture of embryonal tissues are supposedly derived.

5. Embryonal cells retain marked growth potentialities and subsequent tumor development frequently occurs.

Since both gonads arise from the same cell prototypes, embryonal carcinoma of similar stamp in ovary and testicle is readily explained. In teratomas, the carcinomatous fraction outgrows and destroys the other tissue components. Striking examples of one-sided teratomas are seen in chorioma testis and struma ovarii.

Although the pathology of embryonal carcinoma of the gonads has long been known, the histogenesis even to date remains problematic. In the testicle Langhans in 1887 described scirrhus and diffuse forms and ascribed their origin to the spermatic tubules. Wilms in 1898, demonstrated the teratomatous nature of embryonal carcinoma but traced its origin to the spermatic cells in the tubules. In the same year Chevassu described the same tumors as "seminome" deriving it from the spermatoblast. Ewing in 1911 reporting on testicular tumors emphasized the teratoid origin of embryonal carcinoma. In one of his cases minute traces of cartilage were found which "would have been overgrown and eradicated by the rapidly advancing carcinoma." The histologic finding of a lymphoid stroma so frequent in this neoplasm lends additional support to this viewpoint. In the ovary, embryonal carcinoma has for a long time been erroneously reported as large round

*Read at a meeting of the Brooklyn Gynecological Society, April 6, 1934.

cell sarcoma or endothelioma. The largest series of 48 cases has only recently been reported by Robert Meyer. His terminology of "disgerminoma" would emphasize the origin of this tumor from the primitive germinal cells of the genital ridge. These elements remaining undifferentiated lack the faculty of producing masculine or feminine structures. The high incidence of hermaphroditism clinically encountered with this tumor supports this interpretation.

The gross pathology of ovarian embryonal carcinoma is not distinctive. As a rule the neoplasm is unilateral, round or ovoid in form and of varied size. In the early stages the tumor is firm, gray white, and encapsulated. Later, thrombosis and hemorrhage impart a red or bluish tint. Liquefaction necrosis produces areas of softening. On section the opaque appearance is similar to other solid carcinomas. Microscopically, however, a classical picture is present. The cells are large, round or polygonal in form. The cell cytoplasm is scant and the cell membrane poorly defined. The bulk of the cell is filled with a large, round or oval nucleus, vesicular in character and rich in fine chromatin granules. Mitotic figures are not uncommon. As a rule, the constituent cells are loosely arranged in irregular alveoli demarcated by a fibrillar stroma often infiltrated with lymphocytes. The lymphocytes, however, may be lacking in the scant stroma of the diffuse forms.

Clinically, the subjective complaints are those of other ovarian neoplasms. The onset early in puberty is frequent and distinctive. The incidence of true and false hermaphroditism is strikingly high and was encountered in 27 of the 48 cases reported by Robert Meyer. Women free from this stigma, show genital hypoplasia. Growth of the tumor is rapid and progressive. The prognosis is poor although Robert Meyer reports a favorable response to surgery in the early cases. The literature, however, records many cases with extensive metastases at the onset of clinical symptoms.

The following three cases in the Gynecological Museum of the Long Island College of Medicine emphasize the clinical history and pathologic characters of embryonal carcinoma of the ovary:

CASE 1.—Mrs. M. N., aged fifty-one (Museum No. 27:8:1), was admitted to the Gynecology Service of the Long Island College Hospital on Dec. 17, 1932, complaining of pain in the right lower quadrant and irregular menstruation. The past personal history was essentially negative except for resection of a mesenteric cyst and left salpingo-oophorectomy in 1917. Menstruation began at fourteen, recurred regularly every twenty-eight days and continued for four or five days until the onset of the present illness nine months before admission. At that time the patient noticed menorrhagia which gradually increased in severity. For three months prior to admission the bleeding had been constant and was associated with severe pain in the right lower abdomen. There had been a weight loss of 20 pounds in the past year. Physical examination showed an anemic patient of medium stature. Examination of the head, neck, and thorax was essentially negative. The abdomen was enlarged and asymmetrical; the umbilicus everted. In the right lower quadrant there was found a firm mass evidently arising from the pelvis and extending above Poupart's ligament to the level of the umbilicus. This mass was tender and irreg-

ular. The vaginal examination showed a parous introitus with a relaxed pelvic floor and moderate rectocele. The cervix was firm and fixed. The uterus was displaced to the left by the tumor previously noted on the right side of the abdomen. Examination of the blood and urine showed no abnormalities. The blood pressure was normal. On Jan. 7, 1933, exploratory laparotomy was performed. A tumor mass filled the right side of the pelvis and extended upward to the right hypochondrium. The intestines and omentum were so intimately adherent that their separation caused profuse bleeding. Extirpation was therefore abandoned and the abdomen was closed after the insertion of iodoform packs. On Jan. 11, four days after operation bronchopneumonia developed. This was associated with right suppurative pyelonephritis which caused death of the patient on Feb. 22, 1933, forty-six days following operation.

Partial autopsy limited to reopening of the operative wound was performed the same day. The right pelvic cavity was entirely occupied by a round tumor which

Fig. 1.

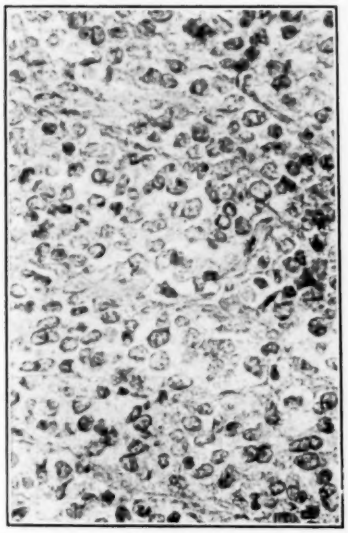

Fig. 2.

Fig. 1.—Case 1. The cut section of the tumor reveals extensive areas of hemorrhage and necrosis. The central and inferior aspects, however, are fairly well preserved. A fibrillar network is just recognizable. The meshes contain opaque tumor tissue.

Fig. 2.—The tumor cells are arranged into irregular alveoli by fine connective tissue trabeculae. The constituent cell is large, almost entirely filled by a large round or oval nucleus which is vesicular in character. There is moderate variation in size, shape, and staining character. (Case 1.) ×350.

upon removal measured 19 by 13 by 12 cm. The mesentery, omentum, small and large bowels were firmly fused with the neoplasm. The right kidney pelvis was markedly dilated and filled with fetid greenish yellow pus. The left kidney was normal. The bladder was the seat of a diphtheritic cystitis. The other abdominal viscera presented no striking pathologic changes. The anterior fundal wall of the atrophic uterus contained three small fibromyomas, varying from 1 to 3 cm. in diameter. Microscopically, the characteristic senile changes of the mucosa and muscle were encountered dependent upon subintimal sclerosis of the nutrient arteries. Focally, metastatic collections of epithelial cells were present but only the endometrial

and muscular layers were involved. The left adnexa previously removed were not available for study. The right tube was normal but the parametrium contained microscopic cell rests with characters essentially those to be described in the right ovary.

This organ was converted into a semisolid, lobulated, ovoid tumor measuring as noted above 19 by 13 by 12 cm. The growth direction was intraligamentous. On the anterior aspect of the tumor the tunica had been penetrated by proliferating tumor tissue which was soft, friable, and hemorrhagic. On the posterior aspect the capsule was retained. On cut section the characters were partially obscured by areas of necrosis and interstitial hemorrhage. Thrombosed vessels were prominent. The central and inferior portions of the tumor were well preserved (Fig. 1). A coarsely fibrillar pattern could be differentiated. The meshes were filled with opaque dark gray tumor tissue. Microscopically, multiple sections of the tumor showed large areas of necrosis in which the morphology could not be dif-

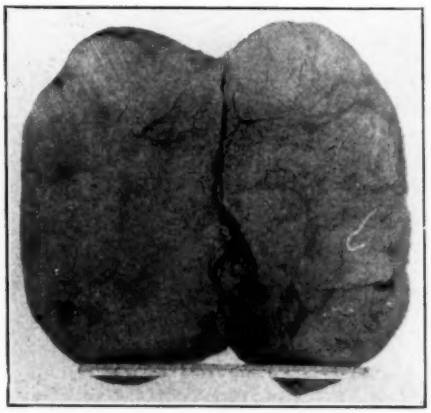

Fig. 3.

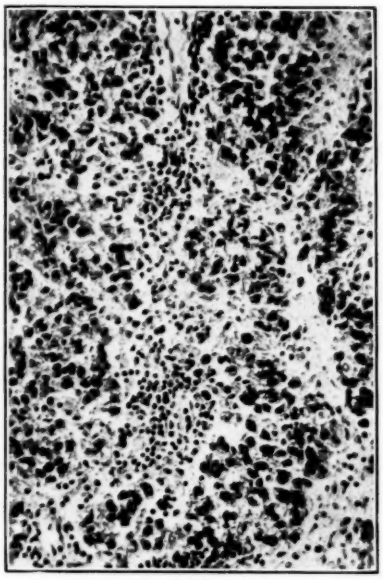

Fig. 4.

Fig. 3.—Case 2. On section the tumor is divided into islands of opaque tissue by well-defined connective tissue trabeculae.

Fig. 4.—The tumor cells are arranged in irregular cords or small alveoli defined by connective tissue septums infiltrated with lymphocytes. The tumor cells are round or oval and almost entirely filled by the nucleus. Lymphoid stroma and the large cell are typical of the lesion. (Case 2.) ×250.

ferentiated. In the preserved zones the tunica of the organ was recognizable. The viable tumor cells were grouped into alveoli of irregular size. Focally, however, the growth was diffuse. The constituent cell was large in size, round or oval in form. The cell membrane was faintly defined, the cytoplasm scant and pale staining. The bulk of the cell was filled by a large round or oval faintly staining nucleus of vesicular character (Fig. 2). Variation in size and staining character was not marked. Mitotic figures were observed with only moderate frequency. Occasionally fusion giant cells were encountered. Sections from the anterior aspect of the growth revealed invasion of the capsule with appearance of neoplastic cells on the surface. Anaplastic characters here were more pronounced, the cells showing greater variation in size, shape, and staining character.

CASE 2.—(Museum No. 27:8:3.) This tumor received in 1914 was found catalogued under "large round cell sarcoma." This history is not available. The tumor ovoid in form measured after fixation 14.5 cm. in length, 8.5 cm. in width and 7.5 cm. in thickness. The external surface was smooth and gray white in color. On section the opaque tumor was divided into irregular islands by bands of connective tissue (Fig. 3). Microscopically, broad trabeculae of connective tissue divided the constituent tumor cells into irregular clusters (Fig. 4). Large numbers of lymphocytes were intermingled with the fibroblastic stroma. The tumor cells proper were grouped into long cell columns, irregular alveoli or broad sheaths. Everywhere, however, the cell morphology was identical. The constituent cell was large, round, or oval in form with moderate acidophilic cytoplasm. The bulk of the cell was occupied by a large well-staining nucleus which was round or oval in form. The chromatin content was high but the vesicular character was nevertheless retained. Mitotic figures were numerous. Variation in size, shape, and staining characters were frequent. Focally, coagulation necrosis had occurred. In these areas neutrophiles and occasional eosinophiles had appeared in the surrounding stroma.

CASE 3.—Miss M. B., aged thirteen (Museum No. 27:8:4), was admitted to the Long Island College Hospital, June 30, 1931, complaining of enlargement of the abdomen and fever. Menstruation had not as yet appeared. Marked asthenia had been noted for three months. Increase in the size of the abdomen had been present for one month and was associated with progressive respiratory embarrassment. Two weeks later pain appeared. This was confined to the lower abdomen and was cramplike in nature but never intensive. Temperature elevation appeared two days prior to admission. The examination of the head and neck was negative. The thorax showed diminution of the respiratory excursion with occasional râles over both bases. The abdomen was enlarged, distended but generally symmetrical. The abdominal wall was 3 cm. above the level of the costal margin. The lower abdomen contained a tumor evidently originating in the pelvis and reaching 4 cm. above the umbilicus. There was no tenderness or peritoneal rebound. A fluid wave was present. On inspection the external genitalia were normal. The hymen was intact. Rectal examination revealed a tense, cystic mass filling the culdesac. The internal genitalia could not be differentiated. Secondary sex characters had not yet appeared. The urine presented an occasional hyaline cast. Examination of the blood showed hemoglobin 50 per cent, red blood cells 2,750,000, white blood cells 11,400, and neutrophiles 85 per cent. The sedimentation time was five minutes. A diagnosis of papillary cyst adenocarcinoma with peritoneal metastases was made. On July 2, 1931, operation was performed under ether anesthesia. The abdominal cavity contained a quart of blood-tinged serous fluid. Lying directly beneath the abdominal wall was a large gray tumor measuring about 15 cm. in diameter. The anterior and lateral surfaces were free. Several loops of small intestine, however, were intimately adherent to the posterior surface. The relation of the tumor to the adnexa could not be clearly established. The omentum was injected and infiltrated with numerous small, friable metastases. Operative removal was abandoned. The abdomen was closed without drainage. Immediately following operation the temperature rose to 104° F. Morbidity persisted for two weeks, the temperature gradually returning to normal. The patient, however, pursued a gradual downhill course and died forty-four days after operation.

Autopsy performed Aug. 15, 1931, was limited to incision through the operative abdominal scar. The abdomen contained abundant serosanguinous fluid. The intestines were displaced upward by a large tumor mass firmly fused with the omentum. The tumor was irregularly lobulated, gray white in color and focally softened and hemorrhagic. The liver showed metastatic growths. The left kidney was enlarged and its upper pole was the seat of a metastatic tumor measuring

about 5 cm. in diameter. Omentum and parietal peritoneum contained metastatic deposits. The uterus was pubescent in type and showed no abnormalities. The left tube was normal, the left ovary elongated and crescent shaped. The right tube was moderately elongated and thin. The right ovary had been converted into a semisolid ovoid tumor mass measuring 18 cm. in length, 12 cm. in width, and 3.5 cm. in its anteroposterior diameter. The tunica of the organ was thickened and preserved except at the superior pole where adhesions of the omentum were noted. On section the tumor was dark gray in color, opaque and presented a distinct fibrous mesh filled with opaque tumor tissue (Fig. 5). In the superior pole a group of four adjacent cysts was encountered. These averaged about 2 cm. in diameter and were filled with opaque thick yellow fluid, probably the end-stage of liquefaction necrosis. In the lower half, opaque gray green areas were noted which represented zones of earlier necrosis. Here, too, liquefaction was encountered. Thrombosed vessels were prominent. Microscopically multiple sections through the

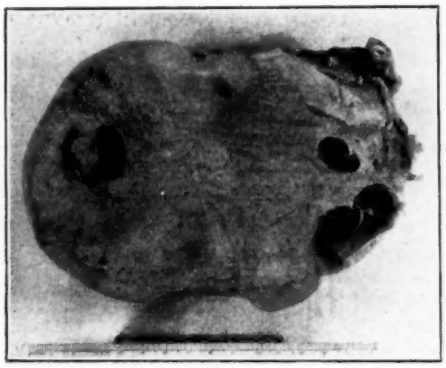

Fig. 5.

Fig. 6.

Fig. 5.—Case 3. Cut section of the tumor shows well-demarcated areas of coagulation and liquefaction necrosis. The central portion is best preserved. A fine fibrillar reticulum is barely recognizable in the opaque homogeneous tumor mass.

Fig. 6.—The tumor cells are arranged in irregular alveoli. The component cells are of relatively large size. The cytoplasm is scant. The bulk of the cell is comprised of a deeply staining nucleus. Variation in size, shape, and staining character is prominent. The supporting stroma is scant. (Case 3.) ×300.

viable tumor zones presented similar characteristics. Fine connective tissue septa subdivided the tumor into alveoli of varying size and contour (Fig. 6). Focally diffuse growth was encountered. The constituent cells of the alveoli presented no definite alignment. They were varied in form, generally round or oval, but fusiform types were occasionally present. The cytoplasm was scant in amount, finely granular and stained lightly with eosin. Cell membranes were not prominent. The nuclei were irregular but generally round or oval in form. They were markedly hyperchromatic and stained deeply but the vesicular character was often retained. Moderate numbers of mitotic figures were seen. In many alveoli lymphocytes were prominent and intermingled with carcinoma cells.

SUMMARY

Three cases of embryonal carcinoma of the ovary are reported. This neoplasm has its exact prototype in the male gonad. Its origin is from embryonal cells of the genital ridge. Teratoid derivation cannot be excluded. Clinically there are no outstanding characteristics but onset early in puberty is frequent. The gross appearance is similar to other solid carcinomas. The histologic picture, however, is distinctive. Large cells with prominent nuclei, supported by a lymphoid stroma produces a classical picture. Diffuse alveolar forms with scant stroma and no lymphocytes have been confused in the older literature with large round cell sarcoma and endothelioma. The prognosis is grave.

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# THE EFFECT OF CIGARET SMOKING DURING PREGNANCY UPON THE FETAL HEART RATE

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THE importance of permeability of the placenta to certain substances and not to others is emphasized by Schlossmann's[16] excellent review of the literature dealing with placental exchange. While we are accustomed to think of the placenta primarily as an organ through which an interchange of nutritive elements from the mother's blood and waste products from the fetal circulation takes place, we may not always appreciate the highly selective nature of this interchange. By reason of this selectivity, the placenta appears to have in addition to functions of nutrition and waste interchange, a protective function. Thus, while a large number of substances pass readily from maternal to fetal circulation in animals, there is evidence that others such as, for instance, bacteriophage, adrenalin, and iron ammonium citrate, do not.

Among those substances about whose transmission across human placental membranes little is known, is nicotine. Because of the recent greatly increased use of tobacco among women, the problem arises as to whether or not the toxic products of the smoke reach and affect the developing fetus if tobacco is used during pregnancy. The work of Tonn,[21] who found nicotine in the milk of mothers whose infants showed evidence of what he believed to be nicotine poisoning, has heightened our interest in the possibility of the prenatal effects of this drug.

If the human placenta is readily permeable to nicotine and other toxic products of tobacco smoke, we might expect to be able to demonstrate them in the umbilical cord blood at birth in those cases where the mother has smoked heavily during the latter months of pregnancy. Sokolov and Lyubovtzeva[19] have shown, however, that animals given large doses of nicotine show a positive blood test for this substance only if the blood is taken within a very short time of the administration of the nicotine. By means of a biologic test for nicotine, consisting of the determination of the effect of the test solution upon the leg muscle of a frog (which is sensitive to 1 part nicotine in 500,000), they were able to demonstrate nicotine in blood taken a longer time after the drug had been administered. Even this very delicate test became negative, however, when the blood was taken a few hours after the nicotine had been injected into the animal. From this work, the difficulties of attempting to determine whether nicotine passes into the fetal circulation by means of an analysis or test of the fetal blood at the time of delivery are apparent. Women do not, as a rule, smoke cigarets during the last few hours before labor. Because of this difficulty, an attempt to determine the presence or absence of nicotine in the fetal blood by measuring any physiologic effect which it might have, has been undertaken. A survey of the literature dealing with the physiologic effects of tobacco convinced us that if the toxic products of tobacco combustion pass into the fetal circulation, some effect upon the rate of the fetal heart might well be expected. Rech[15] has demonstrated the permeability of the human placenta to amyl nitrite by this method.

### PHYSIOLOGIC EFFECT OF TOBACCO SMOKING UPON THE ADULT HEART

There is considerable difference of opinion as to the harm which may result from the use of tobacco. There is, however, a great deal of evidence that the nicotine absorbed from tobacco smoke does cause variation from normal in the physiology of the cardiovascular system, whether or not these variations are harmful. Lee,[9] Fisher and Berry,[5] and Bates[1] state there is rise in blood pressure which in experienced smokers is gradual and in novices is sharp. Schrumpf-Pierron[17] has observed extrasystoles apparently resulting from excessive use of tobacco. Neuhof[12] has reported a case of sinoauricular block which he believes to be due to tobacco poisoning. Siebert[18] states that the larger number of cardiac neuroses he observed during the war were of nicotine origin. Hett[7] in testing the effects of nicotine in the frog heart, found tachycardia the usual effect after a short period of decreased rate. Clerc and Pezzi[2] found a similar effect on the excised mammalian heart. Parkinson[13] found an increase in pulse rate, from four or five cigarets, of about 9 beats. Fisher and Berry,[5] and Bates[1] also have found a consistent increase in pulse rate immediately following the use of tobacco.

The effect upon the cardiac rate is one upon which most investigators are agreed. Although we have not repeated this work on the effect of tobacco on the adult heart rate in any large series of cases, we have made 22 tests on a total of 5 subjects. In this group, we have found

increases in cardiac rate from 5 to 40 beats as a result of smoking. In these cases, the pulse rate became affected in from thirty seconds to one and one-half minutes after the smoking was begun, and persisted for from five to twelve minutes after the cigaret was finished. The persons upon whom these tests were made were all smokers, using from 2 to 10 cigarets per day. The effect upon the heart rate was not noticeably different in the 2 patients who habitually smoked 10 cigarets daily than it was in the 3 who smoked 4 or less daily.

Whether these effects on cardiac rate and those described by other investigators already mentioned are due to the nicotine or to other toxic products in the tobacco smoke is not positively known.

According to Lehmann,[10] Le Bon,[8] Pictet,[14] Lehmann and Gundermann,[11] Trillat,[22] Droit,[3] Fleig,[6] and others, tobacco smoke contains in addition to nicotine the following poisons: pyridine, thiotetrapyridine, isodipyridine, prussic acid, pyrolin, ammonia, collidine, formaldehyde, and carbon monoxide. It is the consensus of opinion of most investigators of the subject, however, that these substances are present in too small quantities to have a demonstrable physiologic effect. Lee,[9] Van Leeuwen,[23] and Lehmann,[10] have proved that the effects of smoking are due practically entirely to the nicotine content of the smoke. They do not feel that other toxic products are present in great enough concentration to cause changes in either heart rate or blood pressure.

## METHOD OF SECURING FETAL HEART RECORDS

Our observations were made by means of a stop watch and a stethoscope placed upon the maternal abdomen at the point where the fetal heart sound could be heard most clearly. In place of counting the number of beats heard during a given length of time, as is commonly done, we measured the time which elapsed during the counting of ten beats. A table was then constructed by which the elapsed time for ten beats could instantly be converted into the rate per minute of the fetal heart. The count was as follows: as soon as a few beats had been heard to establish the rhythm of the beat, the stop watch was snapped on at the point of maximum intensity of a fetal heart sound. As the watch was snapped on the count was started as 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, ending at the point of maximum intensity of the sound on which the count ten was made. An assistant was employed at all times to record the results of the determinations.

We feel that the method is subject to considerably less error than is the fractional minute method in which there is error from the confusion of fractional beats, which sometimes must be dealt with when counting heart beats for a given length of time. Since only ten or twenty beats are counted by our method, any interference with the perception of fetal heart, such as uterine souffle, movement of gas in the intestines, etc., can invalidate only a very short period of the record. By the use of the ten on beat method, the inaccuracies resulting from fatigue and confusion when counting a rapid fetal heart for a minute or half minute are eliminated.

The accuracy of the investigator who made the determinations of fetal heart rate was checked by having him count, and time in a similar manner clicks of a known frequency (from 120 to 180) which were sent through an ordinary telephone headset. During several hundred of these checks, the time recorded for ten of these clicks did not vary more than one-tenth second from the actual elapsed time of ten clicks. A second check was made by having two individuals record the rate of the same fetal heart at the same time. It was found that the difference between the results

of the two investigators was never more than one-tenth second. The limits of accuracy of any individual record was therefore from 1 to 3 beats, according to the rate of the heart. With 6 to 9 samples being taken per minute, the errors tend to become compensated, and the accuracy of the average rate per minute is much higher than that of any individual sample.

### DISCUSSION OF STATISTICAL TREATMENT OF MATERIAL

To use the statistical method advisedly in a study of this nature, the variables under consideration must satisfy certain conditions. Ebbinghaus[4] has criticized the indiscriminate use of the statistical method and gives several criteria for determining whether this method is applicable to the data of a given experimental problem. The first consideration concerns the distribution of the samplings about the mean. Only normal distributions are applicable to this treatment. If it is skewed considerably ordinary statistics will give distorted and unreliable results. Hence a determination of the distribution of the samplings of the heart rate about the mean is not misplaced in this study.

In order to determine the validity of our data, the distribution of the first 2,200 control samplings on the first two patients were plotted. The resulting curves deviated less than the sampling error from the probability curve. The data are therefore applicable to statistical analysis.

The method of procedure of the experiment was as follows: Records of fetal heart during smoking were secured from five subjects. Fetal heart rate samplings were taken for a minimum of five minutes before lighting each cigaret, and for at least fourteen minutes after. Four of the five subjects were habitual cigaret smokers, while the fifth (Subject E) had not smoked previous to undertaking it for our experiment. From this data the mean values of the fetal heart rate for each minute were calculated for each of the 81 records. The average rate for each minute before and after the start of smoking was then calculated and the values plotted in Fig. 1. As is seen in this chart, the maximum effect occurs during the period from the seventh to the twelfth minute following the beginning of the smoke. The effect during the period for each of the five subjects is analyzed in Table I.

The average increase in fetal heart rate after smoking, as shown by the chart, is 5.0 ± 0.19 beats. Since the difference between the rate during the control period

TABLE I. THE EFFECT OF MATERNAL SMOKING ON FETAL HEART RATE

| SUBJECT | NUMBER OF RECORDS | FETAL HEART RATE BEFORE SMOKING MEAN ± $PE_M$ | FETAL HEART RATE 8-12 MIN. AFTER BEGINNING SMOKING MEAN ± $PE_M$ | CHANGE ± $PE_D$ |
|---|---|---|---|---|
| A | 32 | 141.3 ± 0.23 | 149.0 ± 0.27 | 7.7 ± 0.35 |
| B | 18 | 144.0 ± 0.32 | 151.2 ± 0.36 | 7.2 ± 0.48 |
| C | 1 | 140.5 ± 0.49 | 146.5 ± 1 22 | 6.0 ± 1.31 |
| D | 20 | 148.0 ± 0.24 | 150.8 ± 0.22 | 2 7 ± 0 33 |
| E | 10 | 145.4 ± 0.44 | 140.3 ± 0.38 | 5.1 ± 0.57 |
| Average | | 144.0 ± 0.14 | 149.0 ± 0.13 | 5.0 ± 0.19 |

and the rate for the five minutes following the cigaret is more than 25 times the probable error of the difference, there is ample statistical evidence for our conclusion that maternal cigaret smoking does increase fetal heart rate.

Of the five subjects studied, Case E consistently showed a decrease in fetal heart rate following smoking, while all of the others showed an increase. This difference, may, of course, be due to any one of a number of things. We have felt that it was most probably due to the fact that the subject had not smoked previous to this experiment and therefore went through the mechanics of smoking very poorly. Unlike the other four, she did not inhale. Her smoking consisted of filling her mouth with smoke and then expelling it as quickly as possible. It is probable that the amount of toxic material absorbed from the smoke under these circumstances was very much less than that in the cases of those who inhaled the smoke and retained it for a much longer period. This explanation is in agreement with the findings of others who have investigated the effect of tobacco on the adult heart rate. Sollmann[20] states that small doses of nicotine cause slowing of the heart while larger

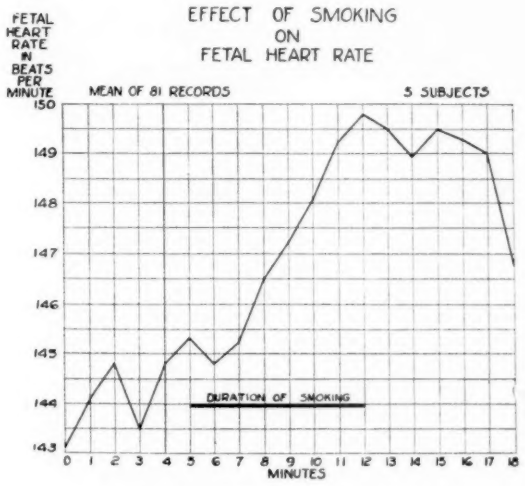


Fig. 1.

doses accelerate it. Parkinson[13] found that experienced tobacco users who inhaled the smoke showed an increase in heart rate, but that those who did not inhale frequently showed no increase and sometimes a decrease in heart rate.

Among the records of the remaining 4 patients, there are scattered instances of individual negative results. While not all 81 of the patients have been analyzed individually in order to make available the mean heart rate before smoking and after smoking for each trial, such data are available for the first 12 trials on Case A. In this series there are two negative results. While the mean of the heart rate before smoking in those 12 trials was 140.2 ± 0.20 beats, the means of the periods before smoking of the two negative trials were 151.7 ± 0.77, and 154.0 ± 0.63. It is evident that during the control period for both the negative trials the rate for some reason was more rapid than it was over the period as a whole. This situation would suggest that the fetal heart rate in these patients had been stimulated to an increased rate previous to the beginning trials, and that since the rate had been raised from 11 to 14 beats above its normal, it tended to subside when the effect of the unknown stimulus wore off. The fact that a fresh stimulus (the products of the tobacco

smoke) which would normally increase the rate from 4 to 7 or more beats, came into action at this time, would not be sufficient to maintain or increase the accelerated rate.

## SUMMARY

A study of fetal heart rate before and after maternal smoking has been made a total of 81 times on 5 patients. The object of the study has been to determine the effect, if any, of maternal smoking on fetal heart rate. It was felt that if fetal heart rate was altered by maternal smoking, this change would indicate that the toxic products of tobacco smoke do pass through the human placenta and enter the fetal circulation. The results of the observations are as follows:

1. The average fetal heart rate for five minutes before smoking was 144.0 ± 0.14. The average fetal heart rate for the eighth to the twelfth minute after a cigaret was lighted and smoking begun, was 149.0 ± 0.13. The average increase in the rate was 5.0 ± 0.19 beats. Since the difference in rates before and after smoking is more than 25 times the probable error of the difference, the effect of smoking is actual.

2. Of the 5 patients, 4 showed an increase in fetal heart rate after smoking, while the fifth showed a decrease. The 4 showing increases were habitual smokers who inhaled the smoke. The patient showing decrease had never smoked before, did not inhale, and expelled the smoke from her mouth as quickly as possible.

3. There were occasional negative trials in each of the 4 patients showing increase. These occurred for the most part at times when the fetal heart rate during the control period was above its average.

## CONCLUSIONS

1. There is a definite and real effect of maternal smoking upon the rate of the fetal heart.

2. This increase appears to be due to the passage of the toxic products of tobacco smoke into the fetal circulation where they affect the fetal heart rate in the same way that adult heart rate is affected.

3. Since the toxic effects of tobacco upon young children and of nicotine contained in mothers' milk on nurslings have been reported, a careful study of the newborn offspring of mothers who smoke heavily during pregnancy is indicated. Evidence of injurious effects of smoking during pregnancy may be overlooked.

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# OVARIAN FOLLICULAR HORMONE EFFECTS ON THE OVARIES

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BENEFICIAL results have been reported by Lewis, 1933,[1] from therapeutic use of ovarian follicular hormone (theelin, amniotin) in the treatment of gonorrheal vaginitis in children. He observed the effects of the treatment during the course of the infection by frequent examination of the vagina with the usual smear technic, and studied the reaction of the vaginal epithelium to this hormone in histologic sections of small pieces removed at biopsy.

The reasoning which prompted the use of this treatment was decidedly logical. During the last few months of gestation rapid growth occurs in the genital tract of the female fetus. This has been attributed to the large amount of theelin (or theelol) in the blood of the fetus. Increasing amounts have been demonstrated in the placenta, maternal blood, and urine as gestation progresses. Positive tests for this hormone have been obtained from umbilical cords at term and from cord blood. Therefore, the genital tract of the fetus is subjected to an extremely high concentration of this female sex hormone. During the first month or two of postnatal life the genital tract retrogresses, particularly the uterus, which decreases in size. It is known that after parturition theelin rapidly disappears from the blood of the mother. The rate of excretion in the urine also rapidly declines, amounts being too small to detect on the third or fourth day after delivery. There can be little doubt that separation of the fetus from the placenta at birth ushers in a period of relative theelin deficiency in the blood of the newborn. This results in a withdrawal of the genital growth stimulus, which is followed by a period of involution in both vagina and uterus. This question is reviewed with citations to the literature in Chapter IX, *Sex and Internal Secretions* (Allen, 1932).[2]

It seems logical that at such a time the vagina may be more susceptible to infection by gonococcus than if its tissues were in a well-sustained phase of physiologic activity. It has been adequately demonstrated in

several species of mammals that the ovarian follicular hormone induces the growth, which thickens the vaginal epithelium, and stimulates development of the glands of the uterus, both fundus and cervix. Therefore, the therapeutic use of theelin in infants and young girls should bring these organs into a phase of growth and heightened function and enable them to better combat a gonorrheal infection.

The removal of small pieces of vaginal epithelium at occasional biopsies during the course of hormone treatment of children has demonstrated that this is what actually happens (Lewis, 1933).[1] With the rapid growth of the vaginal wall there is a disappearance of gonococci from the vaginal smears.

One criticism leveled against this therapy, however, was that it might have a harmful effect upon the ovaries, which might result in decreased function during later life. Several investigators have reported marked inhibition of growth of ovaries of rats following the injection of ovarian follicular hormone (Doisy, Curtis and Collier, 1931;[3] Leonard, Meyer and Hisaw, 1931;[4] Katzmann, 1932[5]). Before extensive use of theelin in children the possibility of injury to the ovaries should be tested in young primates. Therefore, a series of experiments with monkeys was planned in which the doses injected were proportionate to those used by Lewis in his patients. These experiments have been continued for periods considered to be adequate for the treatment of gonorrheal vaginitis in infants and young girls.

## EXPERIMENTAL PROCEDURE

Six immature female monkeys (*Macacus rhesus*) were used, three for experimental purposes, and three at the same stage of development for controls. They ranged in body weight from 2,085 to 2,425 gm.; the smallest was 15.5 months old and the largest probably slightly over two years of age.

Laparotomies were performed before beginning injections, and measurements of the ovaries and uterus made as additional control observations. Then subcutaneous injections of follicular hormone were begun. To insure maintenance of the hormone level, two injections were given daily. The treatment was continued for twenty-eight days in each of two monkeys, and for thirty-nine days in a third. In the first two animals injections were begun with doses of 20 rat units daily, gradually increased to 70 rat units on the twenty-first day, and continued at this level until the twenty-eighth day; the total dosage exceeding 1,390 rat units. In the third monkey a beginning daily dose of 35 rat units was increased by stages to 80 rat units on the thirtieth day and continued at this level through the thirty-ninth day; the total dosage exceeding 2,382 rat units. The hormone used was "Amniotin," assayed at 50 rat units per c.c.*

The effects of the injected hormone were followed by observations of the reddening and swelling of the "sexual skin" around the external genital organs, on the back of the thighs and base of the tail, as previously described (Allen, 1927[6] and 1928[7]). The question of excretion of hormone from possible overdoses was stud-

*Grateful acknowledgment is made to E. R. Squibb & Sons and Dr. John F. Anderson for supplying this preparation.

ied by testing extracts of overnight samples of urine for theelin content. Thirty-three tests were made in ovariectomized rats. Extracts of several samples of feces ranging in amounts from 10 to 25 gm. were also tested.

At the end of the injection treatment each animal was operated upon and the ovaries and uterus measured for comparison with the control measurements of the same organs. Then the right ovary and uterine tube were removed for study of possible immediate harmful effects. The left ovary and tube and the uterus were left intact for recovery periods of thirty days and removed later at autopsy for histologic study, along with other organs and glands of internal secretion.

## OBSERVATIONS

At the beginning of the experiment the "sexual skin" was pale and not swollen, for the monkeys were sexually immature. The uteri were small and anemic. The ovaries were small, pearly white in color, and contained no superficial follicles large enough to be visible from the surface (see Table I).

TABLE I. BODY WEIGHTS (IN GRAMS) AND MEASUREMENTS (IN MILLIMETERS) OF UTERI AND OVARIES (1) BEFORE AND (2) AFTER INJECTIONS, AND (3) AFTER A MONTH'S RECOVERY PERIOD

| MONKEY | DATE 1933 | BODY WEIGHTS | UTERUS | RIGHT OVARY | LEFT OVARY |
|---|---|---|---|---|---|
| C (1) | 4-12 | 2,085 | 8.5 × 3 | 6 × 4.5 × 3 | 6 × 4.5 × 3 |
| C (2) | 5-15 | 2 255 | 16 × 11 | 5 × 4.5 × 2.5 | 5 × 4.5 × 2.5 |
| C (3) | 6-14 | 2,410 | 12.5 × 6 | | 5.5 × 4.5 × 3 |
| NC (1) | 4-12 | 2,425 | 10 × 4.5 | 8 × 5.5 × 4 | 9 × 5 × 4 |
| NC (2) | 5-15 | 2,655 | 15 × 14 | 8 × 4.5 × 4 | 8 × 4.5 × 4 |
| NC (3) | 6-14 | 2,780 | 11.5 × 7 | | 8.5 × 4 × 4 |
| SM (1) | 4-26 | 2,300 | 7.5 × 3 | 7.5 × 3.5 × 2 5 | 7.5 × 3.5 × 2 5 |
| SM (2) | 6- 5 | | 17 × 12 | 7.5 × 3 × 2.5 | 7.5 × 3 × 2.5 |
| SM (3) | 7- 8 | 2,740 | 12 × 6 | | 8 × 4.5 × 2 |

Effects of the injected hormone were first evident in reddening and swelling of the "sexual skin." As injections were continued these secondary sex characteristics were intensified. Toward the end of the experiment the areas affected averaged 13 by 10 by 4 cm. Within from seven to ten days after cessation of injections the color had faded and the swelling regressed to control conditions. Judging from previous experience with this "sexual skin" reaction, an effective level of hormone concentration was maintained during the course of the experiment.

A second indication of maintenance of a continuous high level of hormone was the decided increase in size of the uteri during the course of injections. A comparison of the first and second measurements of the uterus of each animal in Table I shows an average increase of 7 by 9 mm. in anteroposterior and lateral diameters at the uterotubal junction. In monkeys C and NC these increases were obtained in twenty-eight days and in monkey SM in thirty-nine days.

Thirty-one of the 33 analyses of overnight samples of urine were negative and two were positive. No positive results were obtained from tests of feces. Therefore, the matter of injection of more than threshold doses need not be considered.

Immediately after cessation of injections one ovary and tube were removed from each animal, other genital organs being left intact for an interval of thirty days for recovery from hormone effects. Measurements of the uteri after the recovery period showed much involution, but after thirty days without ovarian hormone influence, other than that from the single immature ovary, the uteri were larger than at the beginning of the experiment.

Measurements of the ovaries (Table I) before and immediately after the injection treatment showed a slight decrease in size after hormone treatment. After recovery periods of thirty days following cessation of injections, the left ovaries in two monkeys had not regained their full control size. In the third monkey (SM) there was a slight increase over the control measurement. Some compensatory hypertrophy of the second ovary might have been expected after removal of the first, but it is probable that it would not be great until the approach of sexual maturity. That injected animals were still decidedly immature was shown by rapid involution of "sexual skin" phenomena and decreased size of the uterus during the thirty-day period following cessation of injections.

The ovaries were sectioned serially and compared with the controls in a further search for possible harmful effects. The first impression to be noted was that growth of follicles with antra (large) had not progressed in the ovaries as far in injected animals as in those of the controls. There were still present, however, normal follicles of all stages of development typical for immature ovaries. The supply of small cortical follicles was equally plentiful in control and experimental animals.

To analyze more thoroughly the follicular content of these ovaries, a census was taken of normal and atretic follicles. This census is summarized in Table II. It includes as a first class the larger normal follicles in which secretion of liquor folliculi had progressed to the point of formation of definite antra. Included in a second class were small follicles in which ova were surrounded by two or more lay-

TABLE II. INCIDENCE OF NORMAL AND ATRETIC FOLLICLES IN OVARIES OF MONKEYS AFTER INJECTIONS OF OVARIAN HORMONE (AMNIOTIN) AND AFTER THIRTY-DAY RECOVERY PERIODS

| MONKEYS | OVARY | TYPES OF FOLLICLES | | | |
|---|---|---|---|---|---|
| | | NORMAL | | ATRETIC | |
| | | LARGE | SMALL | LARGE | SMALL |
| Control | | | | | |
| $Y_1$ | Right | 24 | 121 | 10 | 85 |
| 12 | Right | 22 | 188 | 4 | 82 |
| 13 | Right | 10 | 187 | 35 | 79 |
| Experimental | | | | | |
| C | Right | 6 | 49 | 2 | 95 |
| | Left | 20 | 54 | 9 | 109 |
| NC | Right | 30 | 257 | 29 | 282 |
| | Left | 52 | 170 | 25 | 306 |
| SM | Right | 17 | 80 | 8 | 64 |
| | Left | 16 | 121 | 8 | 78 |

ers of follicle cells, but in which secretion of liquor folliculi had not begun. Atretic follicles were similarly classified. The three control animals appear first. The right and left ovaries of the experimental animals should be considered separately. The right ovary in each case was removed immediately after the series of injections of follicular hormone, the left remained in the animal for a recovery period of thirty days.

It seems clear from a consideration of these data that no serious damage has been done to these ovaries as regards the number of normal follicles present. The proportion of normal to atretic follicles shows little significant variation when the two ovaries of each injected animal are compared. When the injected animals are compared with the controls there seems to be at least a temporary increase of follicular atresia.

This statement, of course, would apply only to the dosage given over the intervals covered by this experiment. There were abundant stocks of small follicles through the cortical zones of ovaries of injected animals. The only definite effect which can be discovered histologically was possible interference with the growth of the larger follicles, which would account for the slight decrease in size of the ovaries immediately after the hormone treatment.

## SUMMARY AND CONCLUSIONS

1. Injections of ovarian follicular hormone (amniotin), in doses ranging from 1,265 to 1,390 R. U. over periods of twenty-eight and thirty-nine days, were made into immature monkeys. That this hormone treatment was effective was shown by the reddening and swelling of the "sexual skin" and by increase in size of the uterus.

2. Ovaries were studied for possible harmful effects from this treatment. The first ovary in each animal was removed immediately after a series of injections, the second ovary after a thirty-day recovery period. There was a slight decrease in size of the ovaries removed immediately after the period of injections. A month later the second ovary compared favorably with its control size (some compensatory hypertrophy may have been operative during the recovery period). Decrease in size was due to a smaller number of the largest follicles. A census of normal and atretic follicles in experimental and control animals indicated a slight increase in follicular atresia. There were present in ovaries of injected animals many small cortical follicles and comparable numbers of medium-sized normal follicles in which secretion of liquor folliculi had begun.

3. Therefore, as far as can be ascertained histologically, there seems to be little damage to the ovaries, which would be more than temporary, from injections of follicular hormone (amniotin) in the dosage and over the intervals used in these experiments. The therapeutic use of comparable doses of this hormone in children may be prescribed without fear of harmful results upon ovaries.

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# THE VALUE OF IRRADIATION IN THE TREATMENT OF OVARIAN CARCINOMA*

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IN 1927, Drs. Keene, Pancoast and Pendergrass reported the results obtained from irradiation therapy in 24 cases of inoperable carcinoma of the ovary.† They reached the following conclusions:

1. It is impossible to predict what the effect of irradiation will be on any given patient. This effect will be determined by the first series of treatments; should no benefit be derived, further irradiation is usually a futile procedure.

2. In case of more or less generalized carcinomatosis, in which the primary growth has not been removed, little can be expected from treatment.

3. A decidedly more hopeful outlook, so far as relief from symptoms is concerned, can be anticipated when the primary growth has been removed.

The present study of the results obtained from the postoperative treatment of 38 additional cases confirms these conclusions, except that with the improvement of technic and equipment the prognosis is more favorable for palliation and for the prolongation of life.

This analysis showed that the histologic type of carcinoma is of no value in determining what the effects of roentgen therapy will be. On the other hand, the extension of the growth proved to be of definite prognostic value, and for this reason the patients have been divided into three groups, based upon the degree of involvement at the time of operation (Table I). In the first group, consisting of six patients, complete removal of the affected organ was possible and no visible evidence of the malignancy remained. In the presence of unilateral ovarian carcinoma, the uterus and the opposite ovary should be removed, despite the absence of macroscopic or even frozen section evidence of contralateral involvement.

The second group includes 19 patients from whom the primary growth was removed, but peritoneal metastases were present. The original tumor should be removed when possible, for even in the presence of transplants, this procedure greatly enhances the effect of postoperative irradiation. Frequently the operation alone will be followed by temporary symptom-

*Read at a meeting of the Obstetrical Society of Philadelphia, May 3, 1934.

†The Value of Irradiation in the Treatment of Inoperable Carcinoma of the Ovary, J. A. M. A. 89: 1053, 1927.

atic improvement and retardation of the malignant process, but more prolonged palliation occurs when roentgen therapy is preceded by surgical removal.

TABLE I. TABULATION ACCORDING TO THE EXTENT OF GROWTH

| | | |
|---|---|---|
| | *Patients receiving irradiation* | 38 |
| Group I. | Entire malignant process apparently removed | 6 |
| Group II. | Primary growth removed with transplants remaining | 19 |
| Group III. | Generalized peritoneal involvement | 13 |
| | *Patients operated upon only* | 51 |
| Group I. | Entire malignant process apparently removed | 27 |
| Group II. | Primary growth removed with transplants remaining | 15 |
| Group III. | Generalized peritoneal involvement | 9 |

The third group, numbering 13 cases, is those with generalized carcinomatosis, in whom it was impossible to do more than an exploratory laparotomy and drainage of the ascites. It is our policy to advise abdominal incision under local anesthesia in such cases, for this affords the safest means of removing ascitic fluid and permits the collection of tissue for microscopic study. Occasionally, removal of the primary growth is unexpectedly possible, thereby increasing the chances of favorable response to irradiation. Furthermore, other pelvic tumors may so closely simulate extensive ovarian carcinoma that exploration is necessary for accurate diagnosis.

For comparison we have included 51 patients who were operated upon in the Gynecological Clinic for ovarian carcinoma but who were not given postoperative irradiation.*

The length of life after operation offers the most definite basis for comparing the results obtained in the treated and untreated groups. Of the 38 patients who received roentgen therapy, 21 are now dead and 90 per cent of these lived less than two years following the operation (Table II). All the deaths were in Groups II and III. Of the patients who were not given roentgen therapy, 25 are now dead and 89 per cent of these succumbed in less than two years. Since approximately 90 per cent of the deaths in both groups occurred in less than two years after operation, we have analyzed the treated and untreated patients by using the two-year standard of salvage in addition to the usual five-year standard (Table III).

In Group I, of the four patients who received roentgen treatment, all are living, while 15 per cent of the untreated patients died within two years. This suggests the value of roentgen therapy as a prophylactic measure following apparent complete removal of the malignant disease.

*We are indebted to Dr. Douglas P. Murphy for the use of his follow-up data upon these patients.

In the other groups, the results of irradiation are more definite. Fourteen patients in Group II were treated and four (29 per cent) are alive after two years, while in the untreated cases only two (13 per cent) of 15 patients survived. With generalized carcinomatosis, 25 per cent of the treated patients are alive after two years, in contrast to 11 per cent of those not treated. Finally by combining Groups II and III, we find that 22 per cent of those treated and only 12 per cent of those not treated lived two years or more after operation.

TABLE II. DURATION OF LIFE OF DEAD PATIENTS

| | NUMBER OF PATIENTS | SIX MONTHS TO TWO YEARS | TWO TO THREE YEARS | THREE TO FOUR YEARS |
|---|---|---|---|---|
| *Patients Receiving Irradiation* | | | | |
| Group I | 0 | 0 | 0 | 0 |
| Group II | 12 | 10 | 1 | 1 |
| Group III | 9 | 9 | 0 | 0 |
| | 21 | 19 (90%) | 1 | 1 |
| *Cases Operated Upon Only* | | | | |
| Group I | 4 | 3 | 1 | 0 |
| Group II | 13 | 13 | 0 | 0 |
| Group III | 8 | 6 | 2 | 0 |
| | 25 | 22 (89%) | 3 | 0 |

TABLE III. TWO-YEAR SALVAGE

| | GROUP I | | GROUP II | | GROUP III | |
|---|---|---|---|---|---|---|
| | TREATED 4 PATIENTS | UNTREATED 27 PATIENTS | TREATED 14 PATIENTS | UNTREATED 15 PATIENTS | TREATED 8 PATIENTS | UNTREATED 9 PATIENTS |
| Alive | 4 (100%) | 23 (85%) | 4 (29%) | 2 (13%) | 2 (25%) | 1 (11%) |
| Dead | 0 | 4 (15%) | 10 (71%) | 13 (87%) | 6 (75%) | 8 (89%) |

The five-year salvage is summarized in Table IV. While the greatest prolongation of life follows the use of roentgen therapy in all three groups, it is most significant in Group II, where 43 per cent of the treated patients are alive after five years as against 13 per cent of those not treated. While the number of patients in this study is too small to offer conclusive proof, the results suggest that roentgen therapy does aid in prolonging life.

A comparison of our figures and those reported by Drs. Keene, Pancoast, and Pendergrass shows that improvement in equipment and technic has been followed by better results. Of the 18 patients in Group II which they surveyed, none lived five years, while in the present series a five-year salvage was obtained in three out of seven cases. In Group III none of their patients lived more than one year and in this series, 2 out of 6 patients lived more than two years.

Some may question the wisdom of prolonging the existence of these patients, but if they can be made more comfortable at the same time, there can be no doubt of its justification. That relief of the distressing

symptoms produced by extensive ovarian malignancy frequently follows irradiation is shown in Table V. Twenty patients had severe pain and in 60 per cent of these the pain was definitely lessened or entirely relieved. Ascites was present in 22 and in 36 per cent its reaccumulation was prevented or retarded. Of the 32 patients who had palpable abdominal masses, reduction in the size of the tumor occurred in 31 per cent and in a few they disappeared. In several instances the masses and ascites recurred at varying intervals following the cessation of treatment, and became less responsive to each successive series until eventually the patient succumbed. We are convinced of the palliative value of roentgen therapy. Although the relief is often temporary it is sufficient to warrant treatment even in the presence of advanced ovarian carcinoma.

TABLE IV. FIVE-YEAR SALVAGE

| | GROUP I | | GROUP II | | GROUP III | |
|---|---|---|---|---|---|---|
| | TREATED 1 PATIENT | UNTREATED 27 PATIENTS | TREATED 7 PATIENTS | UNTREATED 15 PATIENTS | TREATED 6 PATIENTS | UNTREATED 9 PATIENTS |
| Alive | 1 (100%) | 23 (85%) | 3 (43%) | 2 (13%) | 1 (17%) | 1 (11%) |
| Dead | 0 | 4 (15%) | 4 (57%) | 13 (87%) | 5 (83%) | 8 (89%) |

TABLE V. THE RELIEF OF SYMPTOMS

| | PRESENT | RELIEF FOLLOWING IRRADIATION |
|---|---|---|
| Pain | 20 | 12 (60%) |
| Ascites | 22 | 8 (36%) |
| Masses | 32 | 10 (31%) |

Forty per cent of the patients in this series experienced severe irradiation sickness, which constitutes the chief objection to this form of treatment. The reactions were especially prone to occur in Group III in which one-half of the patients became extremely ill during the treatments, while one-seventh of those in the other two groups were similarly affected.

It is impossible to predict the effect of roentgen therapy upon a given patient. While the extent of the growth is the best guide to prognosis, it is not infallible as is shown by the following case. Mrs. E. B., aged thirty-seven, was operated upon by Dr. F. E. Keene, on April 6, 1929, for extensive ovarian carcinoma. Microscopic examination revealed adenocarcinoma. A huge quantity of ascites was evacuated and the carcinomatous process was found to be so extensive that removal of the primary growth was impossible. The peritoneum was studded with metastatic nodules. Deep roentgen therapy was begun ten days later and completed in two weeks. Eight weeks later the ascites was again evacuated and a second series of irradiation given. There was no reaccumulation of fluid following this series. Two more series of roentgen therapy were given at sixty-day intervals. In January, 1932, thirty-

three months after the first operation, Dr. Keene repaired a ventral hernia and at the same time he was able to remove the huge primary malignant growth, involving both ovaries. Another series of irradiation was begun ten days later. At the present time, five years after the first operation, the patient is in excellent health with no evidence of disease in the abdomen or pelvis.

### TECHNIC OF TREATMENT

The patients were given irradiation over the primary site, the lymphatics draining it, and the possible peritoneal transplants. Our plan of treatment consisted of administering to the patients in Group III the maximum therapy, depending upon the skin tolerance and the general condition of the patients. This was continued as long as palpable evidence of the disease remained. The intervals between the treatments were extended as long as permissible, in order to preserve the effects of irradiation. This seems to be an important point as it is well recognized that malignant tissue does become radioresistant. One patient received approximately 7,000 r. into the center of the pelvis during a period of five years. Patients in Group II were given two series of treatments at intervals of six weeks, through two, three, or four portals about the pelvis, abdomen, and back, depending upon the size of the patient, and through an additional upper lumbar and lower thoracic portal. Further treatment depended entirely upon the course of the disease. Those in Group I received one series of treatments through the 20 by 20 cm. portals as outlined. A series consisted of 1,600 r. as measured in air delivered to each portal about the pelvis and abdomen and 800 r. to the upper lumbar one. The factors were: 200 KVP. and 4 ma. (since 1932, 165 KVP constant potential and 15 ma.); the filtration was 0.5 mm. Copper plus 2 mm. Al.; and the target skin distance was 50 cm. The treatments were given in divided doses using the saturation method. The rapidity of delivering the dosage depended to a large extent upon the general condition of the patient and the amount of irradiation sickness if such were present.

### CONCLUSIONS

This study shows that in the treatment of ovarian carcinoma, roentgen therapy has a two-fold value: first, the prolongation of life; second, the relief of symptoms as evidenced by its beneficial effect upon pain, ascites, and tumor formation.

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### DISCUSSION

DR. EUGENE P. PENDERGRASS.—All of the cases reported received postoperative irradiation, except one. In that patient, Mrs. E. B., I feel justified in regarding her irradiation as preoperative. If the result can be regarded as indicative of what may happen in patients with inoperable carcinoma of the ovaries receiving preoperative irradiation, it may be necessary in the future to change some of our present concepts as to the best time to operate upon the patient.

We are convinced that removal of the primary malignancy will enhance the value of irradiation. On the other hand, it may be better to give a preoperative course of irradiation after the diagnosis has been established.

The procedure that may come to be the one of choice and suggests itself to me is: (a) operative and pathologic diagnosis; (b) irradiation over the primary malig-

nancy and lymphatic channels draining it; (c) operative removal of the primary malignancy six to twelve weeks later or at such time as the patient's condition may indicate; (d) postoperative irradiation as indicated. I realize that there is only one case upon which to base such an opinion, but the result in this case has been so satisfactory that it deserves further trial. Furthermore, preoperative irradiation may render a lesion, otherwise inoperable, at least palliatively operable.

DR. LEWIS C. SCHEFFEY.—The work described is very much in line with the results reported from the Jefferson Hospital several months ago. From that study I can heartily endorse the conception of following operative treatment with irradiation, and agree that exploratory section should be the primary step, at least.

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# A PHARMACOLOGIC STUDY OF THE UTERINE FISTULA OF THE UNANESTHETIZED RABBIT*

## I. PITUITRIN

GEORGE L. WEINSTEIN, M.A., M.D., AND MAURICE H. FRIEDMAN, M.D., PH.D., PHILADELPHIA, PA.

*(From the Department of Physiology, University of Pennsylvania)*

REYNOLDS (1930) has demonstrated the difference in the uterine responses of the unanesthetized animal to large doses of pituitrin and pitocin. Our study was undertaken to determine more completely the response of the uterine fistula to extracts of the posterior lobe of the pituitary gland and to identify the factor responsible for the difference in uterine response to pituitrin and to pitocin.

### EXPERIMENTAL PROCEDURE

Female rabbits weighing 2.5 to 3.5 kilograms were used in these experiments. Immediately postpartum the young were removed.†

All extract dilutions were made with a tuberculin syringe in normal saline. All injections were made in the marginal ear vein. The pituitary extracts used in this study were pituitrin, pitocin, and pitressin, which were generously supplied by Parke, Davis and Company.

*Record 1.*—Ten minutes elapse between end of Record A and beginning of Record B, a period of uterine inactivity.

1. 0.1 c.c. pituitrin.
2. 0.1 c.c. pituitrin ten minutes after initial pituitrin injection.
3. 0.1 c.c. pituitrin twenty-one minutes after previous pituitrin injection.

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Read at a meeting of the Obstetrical Society of Philadelphia, May 3, 1934.

†The association of regular uterine motility and estrus at this time has been demonstrated by Reynolds and Friedman (1930). The rabbit uterus is bicornuate. Each uterine horn forms a cylindrical hollow tube. The fundal portion of each uterine horn enters the upper end of the vagina. Under ether anesthesia a midline incision was made and the vagina so transected that a small cuff of vaginal mucosa surrounded the orifices of the uterine horns. The orifices of the uterine horns were brought out and sutured to the anterior abdominal wall. Four days after operation a small balloon was inserted into the fistula and by means of a Brody bellows uterine contractions of the unanesthetized intact uterine fistula were recorded on a kymograph (Reynolds and Friedman, 1930).

*Record 2.*—Records C and D are continuous.

1. 0.1 c.c. pitocin.
2. 0.1 c.c. pitocin eleven minutes after previous injection of pitocin.

*Record 3.*—Records E and F are continuous. Five minutes elapse between end of Record F and beginning of Record G.

1. 0.1 c.c. pitocin.
2. 0.1 c.c. pitressin.
3. 0.1 c.c. pitocin twelve minutes after previous pitressin injection.
4. 0.1 c.c. pitocin twenty-eight minutes after previous pitressin injection.

*Record 4.*—Twenty-two minutes elapse between end of Record A and beginning of Record B. Records B and C are continuous.

1. 0.2 c.c. 1:50 pituitrin.
2. 0.2 c.c. 1:50 pituitrin ten minutes after initial pituitrin injection.
3. 0.2 c.c. 1:50 pitocin.
4. 0.2 c.c. 1:50 pitocin nine minutes after initial pitocin injection.
5. 0.2 c.c. 1:50 pitressin eight minutes after previous pitocin injection.
6. 0.2 c.c. 1:50 pitocin eight minutes after previous pitressin injection.

## RESULTS

*A. Injection of a Single Large Dose of Pituitrin.*—The injection of a large dose, 0.1 c.c., of pituitrin (10 international units per c.c.) containing both the oxytocic and pressor factors, produces an immediate uterine tetanus lasting from three to five minutes. This is followed by a decrease in tonus level and complete uterine inactivity persisting from twenty-five to thirty minutes, after which interval the original uterine activity reappears (Fig. 1).

*B. Injection of a Single Large Dose of Pitocin.*—The injection of a large dose, 0.1 c.c., of pitocin produces an immediate uterine tetanus lasting from three to five minutes, and this is followed immediately by large regular uterine contractions with no period of uterine quiescence such as is present after the tetanus following the injection of 0.1 c.c. of pituitrin (Fig. 1).

*C. Injection of a Large Dose of Pitocin Followed by a Large Dose of Pitressin.*—If immediately following the cessation of uterine tetanus resulting from the injection of 0.1 c.c. of pitocin, 0.1 c.c. of pitressin (10 units per c.c.) be injected, there is a rapid loss of uterine motility and the tonus level of the uterus is decreased. Normal uterine activity reappears from twenty-five to thirty minutes after the injection of pitressin. This response to the injection of pitocin followed by pitressin is identical with that obtained on the injection of a single large dose of pituitrin (Fig. 1).

*D. Repeated Large Doses of Pituitrin.*—The injection of a second dose of pituitrin, 0.1 c.c., after the return of normal uterine activity (twenty to thirty minutes) produces a uterine response identical with that originally obtained. However, if the second dose of pituitrin be injected ten minutes after the initial dose, during the period of uterine inactivity, no uterine response is obtained (Fig. 1).

*E. Repeated Large Doses of Pitocin.*—If a similar dose of pitocin, 0.1 c.c., be injected ten minutes after the initial dose of pitocin, a uterine response, identical with that originally obtained, is elicited (Fig. 1).

*F. Large Dose of Pitocin Injected During the Period of Uterine Quiescence Following Injection of Pitressin.*—If a large dose of pitocin, 0.1 c.c., be injected ten minutes after the injection of 0.1 c.c. of pitressin (during the period of complete uterine inactivity), no uterine response is obtained. This failure to obtain a uterine response with pitocin, during the interval of uterine inactivity produced

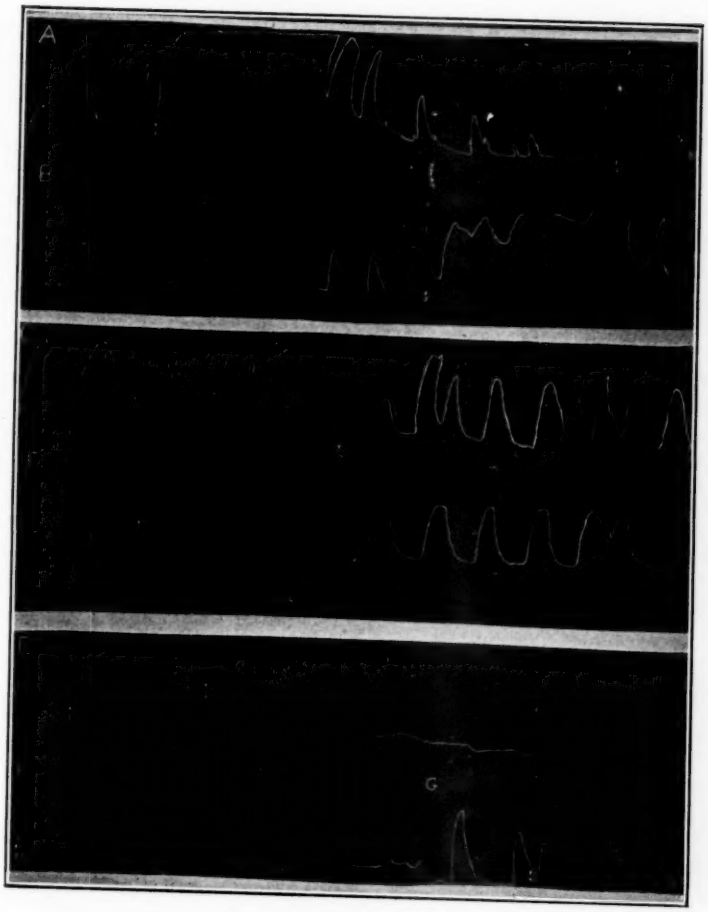


Fig. 1.

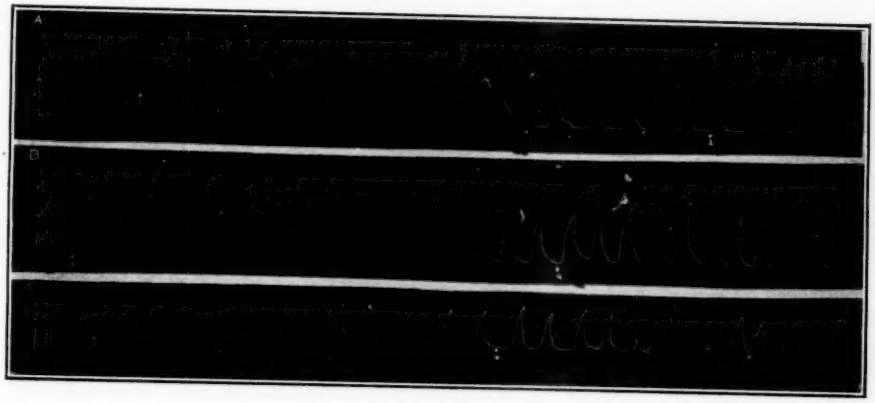


Fig. 2.

by a previous injection of pitressin, is similar to the inability of the uterus to respond to a second dose of pituitrin during the period of uterine quiescence succeeding a previous pituitrin injection (Fig. 1).

*G. Injection of a Small Dose of Pituitrin.*—The injection of a small dose of pituitrin (0.2 c.c. of 1:50 dilution) produces an increase in uterine tonus and an increase in the rate of uterine contractions which change persists from two to four minutes, and then in contrast to the uterine inactivity which is produced by a large dose of pituitrin, the uterine motility quickly returns to its normal character (Fig. 2), i.e., there is no subsequent period of decreased activity.

Nevertheless, the injection of an equal dose of pituitrin ten minutes later, even though uterine motility is normal, produces *no* uterine response; but if twenty minutes elapse between injections, repeated responses, each slightly less than the previous one, may be obtained.

*H. Injection of a Small Dose of Pitocin.*—The injection of a small dose of pitocin (0.2 c.c. of 1:50 dilution) produces an increase in uterine tonus and an increase in the rate of uterine contractions which persists for two to four minutes and is followed by a return to normal uterine motility. This response is identical with that obtained on the injection of a similar dose of pituitrin.

However, in contradistinction to the results obtained with repeated small doses of pituitrin, successive identical uterine responses may be obtained in response to small doses of pitocin (0.2 c.c. of 1:50 dilution) injected at ten-minute intervals (Fig. 2).

*I. Injection of a Small Dose of Pitressin.*—The injection of a small dose of pitressin (0.2 c.c. of 1:50 dilution), immediately after the response obtained with a small dose of pitocin (0.2 c.c. of 1:50 dilution), produces no change in uterine motility. In spite of the fact that no change in uterine motility is produced by this injection of pitressin, the injection of pitocin (0.2 c.c. of 1:50 dilution) ten minutes afterward produces *no* uterine response (Fig. 2). If pitocin is again injected ten minutes later (twenty minutes after the previous pitressin injection) a definite uterine response is obtained.

*J. Tolerance Induced by Repeated Injections of Pituitrin.*—By starting with a small dose (0.2 c.c. of 1:50 dilution) of pituitrin and then injecting successively larger doses at ten-minute intervals, it is found that only the initial injection evokes a uterine response, and following this initial response no further change is produced in uterine motility. This may be continued until the injection of 0.1 c.c. of pituitrin, which normally elicits a maximal uterine response, has no effect either on uterine tonus or motility. This state of induced tolerance to both the oxytocic and uterine inhibiting factors present in pituitrin persists for an interval of sixty minutes following the last injection, after which period the injection of 0.1 c.c. of pituitrin will produce a maximal uterine response.

## DISCUSSION

The results of Reynolds (1930), who first demonstrated the difference in response of the uterine fistula to large doses of pituitrin and pitocin, have been confirmed in this study. Blair-Bell, Datnow and Jeffcoate (1933), using the rabbit uterine fistula preparation employed in these experiments, have also reported that pituitrin, after producing an immediate increase in uterine tonus, induced a temporary inhibition of uterine motility which persisted for an interval of ten to fifteen minutes.

That pitressin is the factor acting to abolish uterine activity after the initial tetanus obtained on the injection of a large dose of pituitrin, is apparent from an examination of Fig. 1. Pituitrin, containing both the oxytocic and pressor factors, causes an initial uterine tetanus followed by a period of uterine inactivity. Pitocin, however, containing only the oxytocic factor, after producing an initial tetanus, does not act to inhibit uterine motility. Pitressin, injected immediately after pitocin, abolishes all uterine activity for an interval similar to that present after the injection of pituitrin. Pitressin must, therefore, be the factor present in pituitrin which so modifies the uterine response to the oxytocic factor present, that uterine quiescence succeeds the initial uterine tetanus.

It may be of further interest to note that in several experiments the injection of pitressin in large doses immediately relaxed the uterine tetanus produced by the intravenous injections of adrenalin, ergotamine, and cocaine. It may, therefore, be said that pitressin will induce uterine relaxation regardless of whether the uterus is exhibiting spontaneous activity or tetanus induced by injection of adrenalin, pitocin, ergotamine, or cocaine.

Previous workers, Frankl-Hochwart, and Fröhlich (1910), and Fühner (1913) have demonstrated a state of uterine tolerance to repeated injections of posterior lobe extract. Bourne and Burn (1927) have noted, on repeating injections of pituitrin in the parturient woman, that no response was obtained to the second injection of pituitrin if the interval between injections was less than one hour. Blair-Bell, Datnow and Jeffcoate (1933) using the rabbit uterine fistula also demonstrated the production of a state of uterine tolerance to repeated injections of pituitrin, the second injection of pituitrin having no effect unless a certain interval of time had elapsed between the first and subsequent injections.

That pitressin is the factor in pituitrin which induces a state of uterine tolerance to subsequent injections of pituitrin is evident from an examination of Fig. 2. After the initial increase in uterine motility produced by a small dose of pituitrin, uterine motility returns to normal. A subsequent injection of pituitrin elicits no response until a certain interval of time elapses between the injections. In contrast to this tolerance, repeated injections of pitocin each produces an increase in uterine tonus identical with that produced by a single, similar small dose of pituitrin. However, the injection of a small dose of pitressin, even though uterine motility is not altered, abolishes all response to subsequent injections of small doses of pitocin for an interval equal to the refractory period following a small dose of pituitrin. It must, therefore, be concluded that the pressor factor (pitressin) in pituitrin is the substance responsible for the failure to obtain repeated uterine responses to a series of injections of pituitrin.

With the injection of large doses of pituitrin, uterine tolerance to a repeated dose of pituitrin apparently was associated, as far as time relationships were concerned, with the period of uterine inactivity follow-

ing the initial tetanus. However, when small doses of pituitrin were injected so that the pressor fraction of the dose of pituitrin injected had *no* influence on uterine motility, it was quite apparent that the uterine tolerance to repeated doses of pituitrin was developed regardless of the state of uterine motility, be it depressed or normal in character.

The production of a state of induced uterine tolerance to both the oxytocic and pressor factors in pituitrin has been demonstrated by injecting successively larger doses of pituitrin at ten-minute intervals. Under this treatment the uterus becomes refractory to both the uterine stimulating (oxytocic) factor and the uterine inhibiting (pressor) factor, so that 0.1 c.c. of pituitrin, which normally elicits a maximal uterine response, has no influence on uterine motility.

The data obtained in these experiments are not in accord with the results reported by Robson (1933) using excised muscle strips of both rabbit and human uteri. In these experiments in vitro, uterine responses were elicited by both pitressin and pitocin. However, the inadequacy of recording and evaluating uterine responses obtained by this method has been discussed by Reynolds (1931) and Van Dyke and Hastings (1927). Blair-Bell, Datnow and Jeffcoate (1933) using the uterine fistula preparation in lightly anesthetized rabbits state that, "Pitressin is quite as effective as a uterine stimulant as is pitocin." In the dose used in their experiments, 0.2 c.c. intravenously, we have repeatedly demonstrated that there is sufficient oxytocic substance present as a contaminant to produce an initial uterine tetanus which is similar to the first portion of the response to pitocin, but in every instance this initial tetanus is followed by a period of uterine inactivity. Adair and Davis (1934) using postpartum women, found no difference in the uterine responses evoked by pituitrin, pitocin, and pitressin. It is quite possible that the dose of pitressin injected contained sufficient oxytocic substance to produce a uterine response in the extremely sensitive parturient uterus. The failure to obtain uterine relaxation after the initial tetanus may be due to a species difference in uterine susceptibility to the uterine relaxing action of pitressin, or to the fact that the dose required for relaxation of the uterus is relatively much greater in the human being than in the rabbit.

Bourne and Burn (1928), however, found that whereas pitocin had a powerful stimulant action, pitressin even in large doses (12.5 International units) had no effect on the uterus in labor. The method of recording used in their work was essentially the same as that used by Adair and Davis.

Although the results of Adair and Davis (1934) with pitressin on the motility of the human uterus are not in accord with the results obtained with pitressin in the rabbit, there is nothing in the results obtained by these workers to indicate that the pressor factor is not responsible for the development of uterine tolerance. There can be little doubt that tolerance to repeated injections of pituitrin does occur in the human uterus, as has been graphically demonstrated by Bourne and Burn (1927). Inasmuch as the development of tolerance in the rabbit is not necessarily associated with any change in uterine motility in either direction, it is entirely possible, if not probable, that the development of a state of

tolerance even in the human uterus is due to the pressor fraction, although the influence of the latter on motility is not identical in the human and the rabbit uterus.

Therefore, since this development of uterine tolerance in the rabbit has been shown to be a property of the pressor fraction of pituitrin, and to be entirely independent of any action it may have on uterine motility, it is suggested that pitocin rather than pituitrin be the drug of choice in the medical induction of labor and in the management of the third stage of labor; at least until more satisfactory data are available on the action of these drugs on the human uterus.

## CONCLUSION

In the rabbit uterus:

1. Large doses of pituitrin produce an uterine tetanus followed by a period of uterine inactivity persisting for twenty to thirty minutes.
2. Large doses of pitocin produce a uterine tetanus followed by normal uterine motility.
3. The uterine quiescence following the initial tetanus produced by pituitrin is induced by the pitressin fraction.
4. Pitressin divorced from its motility inhibiting character by the injection of a minimal dose has been demonstrated to be responsible for the absence of a response to a second injection of pituitrin, unless a definite interval of time elapses between injections.
5. The induction of uterine tolerance is independent of any action of these drugs on uterine motility.

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THIRTY-SIXTH AND SPRUCE STREET

## DISCUSSION

DR. MAURICE H. FRIEDMAN.—There does not seem much to say except that the joke seems to be on us a bit. During the work, we saw this astonishing ability of pitressin to relax the uterus. We could take a uterus, in spasm from any of the drugs that would contract the uterus; we could then by the simple procedure of injecting pitressin, completely relax it. We thought that, perhaps, if it worked like that in the human being, obstetricians and gynecologists would have a valuable aid for use in relaxing the uterus and in the treatment of dysmenorrhea. But this again shows the wisdom of being a bit cautious of transferring results obtained in rabbits to human beings. The conclusion that should be drawn, but from which we refrained, was that the rabbit is, after all, not human.

# A COMPARATIVE STUDY OF LIPIODOL INJECTION AND AIR INSUFFLATION IN STERILITY

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UTEROSALPINGOGRAPHY has now merited a place in the diagnostic armamentarium of the gynecologist.

W. H. Cary first proposed and described a method of testing the patency of the fallopian tubes in 1913 by the transuterine installation of collargol, and the subsequent roentgen ray demonstration of its presence in the peritoneal cavity. Kennedy in 1923 used a 20 per cent solution of sodium iodide. Rubin first used collargol solution and later other opaque media to demonstrate the patency or occlusion of the fallopian tubes. In the past few years lipiodol (40 per cent iodine in a vegetable oil) has displaced these substances in the roentgenologic demonstration of the uterus and tubes. C. Heuser of Buenos Aires described radiography of the uterine cavity with lipiodol and claimed priority for this method, stating that his first report appeared in 1921 and that Wintz and Beclere of France did not mention their work until 1925. S. A. Robins says that uterosalpingography is now applicable not only in sterility but in routine examinations and speaks of it as a simple and harmless office procedure. Darbois and Beclere have widened their indications for the use of uterosalpingography, and utilize it in all their sterility cases to study the patency of the fallopian tubes and to localize any obstruction present. J. Irribane and N. Cappizzane use lipiodol injections of the uterus and tubes in all cases of sterility.

The following technic was employed in a series of 32 cases of sterility as a check on previous air insufflations in the same patients:

The test is performed about ten days before or after the menstrual period. With the patient in the dorsal position and the bladder empty, a bivalve speculum is introduced into the vagina which is wiped dry of secretion. The cervix is painted with tincture of iodine or 2 per cent mercurochrome and is then grasped with a tenaculum. The position, size, shape, and mobility of the uterus is determined previously by a bimanual examination. Patients with any acute pelvic inflammation or marked tenderness of the pelvic organs are deemed unadapted to this procedure. A Keyes-Ultzmann cannula with a rubber acorn on the shaft is introduced into the cervical canal so that the acorn occludes the cervix and prevents leakage. From 8 to 10 c.c. of warmed lipiodol is drawn into a Luer syringe, attached to the cannula, and without undue pressure slowly injected into the uterus. After waiting from three to five minutes with the cannula in situ an x-ray plate is taken, holding the cannula in position during the exposure. A second plate is taken after a five-minute interval. The cannula is removed and the oil wiped out of the vagina. The patient is instructed to return within twenty-four hours for another x-ray plate, to determine the presence of oil in the peritoneal cavity. It has been our experience that the patients with patent tubes have no discomfort and the oil meets with very little resistance during injection.

The technic of the transuterine insufflation test used in our clinic is that described and modified by Dr. Adolph Jacoby. With the patient in the dorsal posi-

tion a bivalve speculum is introduced into the vagina and the cervix exposed. All excess of secretion is wiped away. The cervix is painted with iodine or mercurchrome. No tenaculum is placed on the cervix unless it is necessary to steady and fix the cervix. The Jacoby instrument with a manometer screwed to the side outlet and a 40 c.c. Luer syringe locked at the other end is introduced into the uterine cavity. Care is taken not to traumatize the mucosa. After introduction the obdurator is held tightly against the external os by steady and firm pressure. The piston of the syringe is slowly and steadily squeezed, forcing air through the cannula while the operator watches the pressure indicated on the manometer.

If the tubes are patent, the manometer reading will drop after reaching 100 mm. or more and the air will continue to flow into the peritoneal cavity through the tubes at reduced pressure. In nonpatent cases the pressure will rise to 200 mm. without a subsequent drop. In the patent cases the patient will complain of shoulder pain on arising or soon thereafter.

Thirty-two patients with primary and secondary sterility were examined by both air insufflation and lipiodol injection. In twenty-five of the thirty-two patients examined the findings by air insufflation were confirmed by x-ray after lipiodol injection. In one of these 25 patients, three air insufflation tests were performed; the first test gave a high pressure reading of occlusion; the second test, one of partial obstruction with subjective pain; and the third test showed the tubes to be patent. This patient may have been one of the group in which the therapeutic value of air insufflation becomes evident. Three patients gave readings of occlusion with air insufflation, whereas the salpingogram showed patency. In these, one had three air insufflation tests; one had two air insufflation tests; and one had one air insufflation test. The lipiodol injection was made after the last air insufflation test and one might assume that the tubes may have been opened by the air pressure. Three patients gave readings of partial occlusion with the air test, although salpingograms showed that the tubes were patent. Here the information obtained from the air test was of greater value than that derived from the lipiodol injection. In one patient the air test indicated partial occlusion and salpingogram findings showed the tubes to be closed. In this instance one might suspect that the air could pass through the partially occluded tubes, whereas the greater density of the oil obstructed its passage into the peritoneal cavity. The discrepancy in these seven cases raises the question of the accuracy of the x-ray interpretation. Sometimes the reading of a salpingogram requires a certain amount of presumption on the part of the diagnostician.

Four of the thirty-two patients who had transuterine lipiodol injections performed suffered from subsequent sequelae.

Case 1.—Aged thirty-eight, married five years. Primary sterility. Air insufflation test indicated that the fallopian tubes were patent. On Dec. 16, 1931, a transuterine lipiodol injection was performed and showed patency of the tubes. Several days following the salpingogram patient complained of severe backache. March 31, 1932, patient complained of pain in the left flank and dysmenorrhea which she dated from the time of the lipiodol injection. Vaginal examination showed the fundus and body of the uterus pulled upward and to the left, uterus tender and marked tenderness in the posterior parametrium. April 2, 1932, three and one-half months after salpingogram radiographic report showed a small quantity of contrast medium still present in the pelvis.

Case 2.—Aged thirty-one, married ten years. Primary sterility. Air insufflation test showed the tubes to be patent. Nov. 18, 1931, salpingogram confirmed the air test by report of contrast medium on both sides of the pelvis. Patient com-

plained of pain in the pelvis following lipiodol injection. Dec. 10, 1931, twenty-two days after lipiodol injection radiographic report showed contrast medium to be present in the culdesac.

CASE 3.—Aged thirty-eight, married five years. Primary sterility. Air test showed the tubes to be patent. Nov. 13, 1931, a salpingogram was made. Radiographic report stated that neither tube is definitely visualized but a large globule of contrast medium was seen in the pelvis on the left side. Dec. 3, 1931, patient developed a marked leucorrhea. Pelvic examination revealed a palpable tube and ovary on the right side. Left tube and ovary enlarged to the size of a small apple. April 16, 1932. Five months later a flat plate was taken and the radiographic report showed a quantity of contrast medium on the left side of the pelvis.

CASE 4.—Aged thirty-one, married ten years. Primary sterility. Air test showed the tubes were patent. Nov. 18, 1931, transuterine injection of lipiodol. Radiographic report read "contrast medium seen in peritoneal cavity on both sides," suggesting patency of both tubes. Dec. 10, 1931, radiographic report showed contrast medium in the culdesac approximately three weeks after the injection. This patient came to operation Nov. 17, 1932, about one year after lipiodol injection. Operative findings at the time were as follows: On opening the abdomen a fair quantity of free serous fluid was present. The peritoneal surface appeared to be somewhat irritated. Tubes were found to be normal and patent. The right ovary which was enlarged was resected. The fluid in the abdominal cavity was suctioned off. Surgeon's note: Peritoneal irritation and free fluid in peritoneal cavity is probably accounted for by the previous injection of iodized oil.

TABLE I. THIRTY-TWO CASES OF STERILITY TESTED BY AIR INSUFFLATION AND LIPIODOL*

| | CASES | AVER. YR. MARRIED | YOUNGEST | OLDEST | AIR TEST | | | SALPINGOGRAM AIR TEST AND SALPINGOGRAM | | | SALPINGOGRAM | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | P. | N.P. | P.O. | P. | N.P. | P.O. | POSITIVE | NEGATIVE |
| Primary sterility | 18 | 7.11 | 21 yr. | 38 yr. | 4 | 9 | 1 | 4 | 9 | 1 | 25 | 7 |
| Secondary sterility | 14 | 9.44 | 24 yr. | 41 yr. | 5 | 6 | 0 | 5 | 6 | 0 | | |

SEVEN CASES OF STERILITY TESTED BY AIR INSUFFLATION AND LIPIODOL WITH VARIED FINDINGS

| NO. OF CASES | TYPE OF STERILITY | AIR TEST | | | SALPINGOGRAM | | |
|---|---|---|---|---|---|---|---|
| | | P. | N.P. | P.O. | P. | N.P. | P.O. |
| 7 | Primary | 0 | 3 | 4 | 6 | 1 | 0 |

*P, Patent; N.P., nonpatent; P.O., partial obstruction.
Note: Sixteen of these cases had two or more air tests.

R. J. Heffman in a review of the literature notes that complications consist chiefly of infections but there have also been a number of deaths following the use of salpingography.

W. Odenthal in one of his cases injected 4 c.c. of iodopin (iodized oil), without an immediate reaction, the patient leaving the hospital three days after the injection of the oil, but within ten days she developed symptoms of peritoneal irritation with fever which subsided after three weaks of treatment.

Barton C. Hirst mentions one accident occurring in a woman who urgently requested operation twenty-four hours after a lipiodol test. Distal salpingostomy and suspension of the uterus were performed satisfactorily but a streptococcus peritonitis caused death. It is interesting to note that this operation was preceded by one in which a streptococcus of the same strain was found.

Gauss in a review of the literature states that in about 3,000 cases in which iodized oil was injected there were five deaths and thirteen additional cases of infection.

E. Gajzage reported a case in which death resulted from oil embolism after uterosalpingography, proved at autopsy. The oil was accidentally injected into a vein which was injured at the time the cannula was inserted into the uterus.

I. C. Rubin, whose researches and contributions to the study of sterility are extensive, reported 132 cases in whom lipiodol injections were performed. Six patients developed peritoneal inflammation of a mild grade, and three developed pelvic abscesses requiring surgical intervention. Such results in the hands of a gynecologist of Rubin's experience in this particular field would doubtless prove more serious in the hands of the less experienced.

Joseph L. Baer reports a case in which he had opened the abdomen of an apparently normal patient, free from elevation of temperature, with the intention of doing a Gilliam suspension of the uterus, but in whom he found both tubes dripping free pus from the fimbria. Among other thoughts, he suggests what might have happened had he attempted a patency test in that patient. One can also imagine what might have happened if a lipiodol injection had been made.

The writer had his attention called to a patient, injected with lipiodol by a competent gynecologist, who left his office and upon arriving home was seized with severe abdominal pain. She was removed to a hospital and died a few days thereafter of a fulminating peritonitis.

Emil Ries at a meeting of the Chicago Gynecological Society presented a specimen showing the effect of lipiodol injection on the tubes. This patient was tested for sterility by air insufflation on three different occasions and in each instance the air failed to pass through. This was followed by a lipiodol injection and the x-ray plate seemed to show that the oil had passed into the peritoneal cavity. There was no reaction until two months after the lipiodol injection, when the patient began to feel sick and have pain. She was operated upon and the findings showed extensive adhesions, so that none of the pelvic organs were visible when the abdomen was opened. Both tubes were dissected out and showed an interesting microscopic picture. Large areas of the tubal mucosa had disappeared while elsewhere the lining epithelium was normal. An enormous number of giant cells were present, in the midst of which were found structureless greenish masses of a homogeneous and granular character. Some of the cells contained small particles of this greenish substance. These conditions were found in both tubes; in the open as well as in the closed.

A. F. Lash secured a specimen of bicornate uterus with retention of lipiodol in the pelvis twenty-two months after injection. At laparotomy the omentum was found partly adherent to the right horn of the uterus, to the junction of the two horns, to the bladder and to three masses in the culdesac. After freeing the omentum the three masses which contained lipiodol were removed. Examination of these masses showed no iodine on direct tests, but iodine was demonstrated after breaking down the lipiodol. Lash contends that there was a bilateral salpingitis, with a foreign body reaction produced by the lipiodol, which had been present in the pelvis for twenty-two months.

R. J. Heffman emphasizes the fact that iodized oil preparations may give rise not only to infections but also to fatalities, and that the retention of particles of iodized oil within the tubes may cause local damage.

Barton C. Hirst believes that a lapse of time is essential before operating on a patient who has had a lipiodol injection.

J. Novak insists that salpingography should be reserved for a few special cases. He describes a case in which salpingography showed both tubes to be closed. At operation the tubes were opened and the oil removed, but infection set in and the patient died. At autopsy it was evident that the iodized oil had produced not only inflammatory changes of the tubes but also a foreign body reaction in the peritoneal cavity, and peritonitis. He also mentions another case in which iodized oil was found two years after salpingography. He believes that salpingography should never be used routinely in cases of sterility, and that its use should be limited to rare cases.

Brooke M. Anspach does a lipiodol injection in sterility cases after an air insufflation test has demonstrated a closure, and some operative procedure for its correction is desired by the patient.

Hazelhorst concludes that while uterosalpingography is a valuable method it is not without danger, and he does not consider the presence of free iodized oil in the peritoneal cavity as harmless.

Curtis is of the opinion that the instillation of iodized oil is a valuable procedure but should be used with great caution. He has seen cases in which the peritoneal reactions were very severe.

In view of my personal results in a limited number of cases I believe that despite the simplicity and facility of uterosalpingography, transuterine air insufflation should be the method of choice for the determination of tubal patency in cases of sterility, and that uterosalpingography should be reserved for unusual special cases. With simple insufflation it is easy to determine not only whether the tubes are occluded or patent but also whether one or both tubes are open (stethoscope). In addition, the site of obstruction may be revealed by the localization of pain, and tubal spasm by the use of the kymograph.

Great selectivity and care should be exercised in sterility cases before the injection of lipiodol, and uterosalpingography should be the last step rather than the first in the search for the causative factor of sterility. That the injection of lipiodol is not entirely innocuous and may result in morbidity is substantiated by my own experience and that of others. In the diagnosis and localization of obstruction of the fallopian tubes in cases of sterility, the sequelae may prove harmful to the patient, if the method is applied indiscriminately.

## CONCLUSIONS

1. A review of the literature indicates that routine lipiodol injections are not harmless and that as a diagnostic method it carries a morbidity and mortality, even though small.

2. The use of lipiodol injection in cases of sterility is unwise until a complete history, careful bimanual examination, endocrine survey, air

insufflation tests, study of the vaginal chemistry, investigation of cervical pathology, and the fertility of the male partner have been investigated.

3. Operations on tubes should be postponed for several months after lipiodol injections.

4. In sterility cases in which one tube is occluded or both tubes show partial occlusion as demonstrated by air insufflation, lipiodol injections should be used cautiously, as complete occlusion may result and thus defeat the primary objective.

5. Air insufflation yields the desired information regarding the condition of the tubes, without harm and subsequent sequelae. This has been our experience in a large number of cases.

6. The contention that lipiodol may remain in the peritoneal cavity for one year or more and result in serious pathology has been verified by personal experience and the publications of others.

7. Misinterpretation is not unlikely in the reading of salpingograms by the inexperienced; errors are few after transuterine insufflation.

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**de Torres, E. M.: Oil Embolism in Hysterosalpingography,** Revue franç. de Gynécologie et Obst. **29:** 218, 1934.

Pelvic infection may occur after the use of hysterosalpingography but the most frequent accident is penetration of lipiodol into the blood vessels. In most cases, this accident remains unnoticed because it produces no visible symptoms. An excessive pressure is not necessary to bring about this accident. Among the causes are hypoplasia of the uterus with tubal occlusion and recent hemorrhage. de Torres believes that recent hemorrhage is the most frequent cause. The small open veins permit the ready access of lipiodol which is quickly carried away by the blood stream from the portal of entry. The author, therefore, warns against the use of hysterosalpingography in cases of uterine bleeding. He points out that we have other means of exploring the uterine cavity which are safer, for example curettage. The fact that oil embolism is usually harmless should not be a reason to disregard its possible dangers.

J. P. Greenhill.

# IS THE LOWER UTERINE SEGMENT EXCLUSIVELY A CLINICAL PHENOMENON?

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SINCE the writer in 1928 published a paper[1] on the origin of the lower uterine segment wherein anatomic and histologic evidence was presented to support the contention that the lower uterine segment is made up of both the uterus (or that portion of the nonpregnant uterus designated by Aschoff[2] as the isthmus) and the dilated cervical canal, other articles on the subject appeared, the most notable of which is that of Frankl[3] where among other important data, he makes the same affirmation.

The contention sustained by Frankl[3] and others that the firm attachment of the uterine peritoneum does not correspond mathematically to the upper limit of the isthmus, as originally asserted by Braune,[4] may be true when the differences in the uterine mucosa are made the sole criterion of division between the uterine segments entirely disregarding the muscular disposition or behavior. Nevertheless, I am of the opinion that such an external landmark is—for practical purposes, as for instance in operations on the uterus, the determination of the site of placental implantation or of uterine rupture—of sufficient accuracy to indicate the limit of either the isthmus of the nonpregnant or the lower uterine segment of the puerperal uterus. The lower limit of the isthmus (or lower uterine segment) is also recognizable with the naked eye by the upper border of the arbor vitae or plica palmatae of the cervical mucosa.

## FORMATION OF THE LOWER UTERINE SEGMENT

There has been some confusion in obstetric teaching as regards the formation of the lower uterine segment. When Braune[4] and later, Bandl[5] described what is now known as Bandl's ring and emphasized its clinical importance, denoting the division of the uterus into two segments, namely, superior and inferior, textbooks began to assert that the lower uterine segment is a clinical phenomenon not manifested until labor and only during active contraction of the uterus. At the same time, it was taught, and rightly, that in cases of placenta previa the placenta or part of it is attached to the lower uterine segment which phenomenon a priori presupposes the actual existence of the lower uterine segment at the beginning of pregnancy when placental development takes place. If its existence is denied until labor contractions set in, how could the

placenta be implanted in it? Stieve[6] has clarified this confusion when he showed that during pregnancy, the isthmus uteri, which in pregnancy constitutes the uterine portion of the fully formed lower uterine segment, is gradually drawn up to the ovum chamber. By this he means that the line of constriction separating the corpus from the isthmus uteri is gradually effaced. The examination of specimens at different stages of pregnancy and even during menstruation show that effacement of constriction at the upper end of the isthmus begins to be initiated as early as the pregravid stage when the predecidual formation takes place. Frankl[3] states that from the second month of pregnancy, the limit of the isthmus begins to disappear and becomes unrecognizable in the third month when it fully passes into the upper compartment of the uterus.

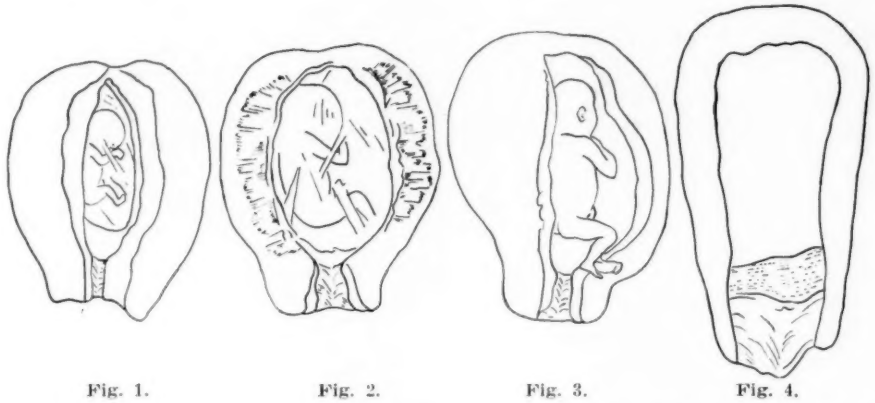

Fig. 1. Fig. 2. Fig. 3. Fig. 4.

Fig. 1.—Two and one-half months' pregnancy. The upper isthmus constriction is erased.

Fig. 2.—Three months' pregnancy. There is no constriction between the upper and lower uterine segments.

Fig. 3.—Three and one-half months' pregnancy. There is no constriction between the upper and lower segment of the uterus.

Fig. 4.—Postpartum uterus showing the relative length of the lower uterine segment and the cervix.

Figs. 1, 2, and 3 show that the isthmus has become part of the ovum chamber and that the only constriction recognizable is the histologic internal os or the upper limit of the cervix.

The above facts conclusively establish that the lower uterine segment, perhaps due to hormonic influences, begins to be formed as early as the implantation of the ovum, and, because it does so, one can understand how it is that sometimes part or most of the placenta may be implanted in it. It is admitted, however, that the complete formation and manifestation of its functional rôle does not take place until the entire cervical canal is completely dilated when the cervix in conjunction with that which was the isthmus takes on a passive or dilative action as a result of effective contraction of the upper uterine segment.

The lower uterine segment during pregnancy and the puerperium can structurally be recognized by its thinner decidua, its poverty in glands which are irregular in arrangement, and the loose disposition of its muscular fibers.

Frankl[3] has shown that no decidua compacta but only the loose decidua spongiosa normally develops from the mucosa of the lower uterine segment. And plausibly he explains that such a condition favors the mobility of the lower pole of the ovum, thus facilitating and rendering bloodless the separation of the membranes during the cervical dilatation and descent of the presenting part. Were the union between the ovum and the uterus in this region intimate as, for instance, in cases of placenta previa, every act of labor would be attended by greater difficulty and perhaps greater amount of blood loss than what ordinarily is observed.

Recent studies of the nonpregnant and puerperal uteri confirm the findings of my earlier paper[1] that the cervix after its complete dilatation forms the greater part of the lower uterine segment. From the evidence shown by the specimens, one can only conclude that during labor the cervix becomes elongated as it dilates so that, when it is completely effaced, it constitutes not the minor but the major portion of the lower uterine segment. This may be verified by examining a uterus that has recently delivered a full-term fetus, measuring that portion which corresponds to the isthmus uteri and comparing it with the portion lined by the glistening cervical mucosa as grossly shown by the plica palmatae. Fig. 4 is a diagram of the uterus of a woman delivered by cesarean section who died four hours after the operation. It shows the relative length of the uterine and cervical portion of the lower uterine segment.

That the cervical canal when completely effaced is longer than the uterine portion of the lower segment should not cause surprise; it is but the natural result to be expected; for, in the normal nonpregnant uterus or the involuting puerperal uterus, the cervical canal is also proportionately longer and is almost, and at times more than twice as long as the isthmus uteri.

The above findings cannot sustain the prevailing opinion among modern authors which, according to Williams, holds that the cervix does not lengthen during labor and constitutes not more than 3 or 4 cm. of the lower portion of the fully formed lower uterine segment. Such a picture, however, seems anomalous for it inverts the natural proportion of the two structures, isthmus and cervix, in the nonpregnant uterus.

## CONCLUSIONS

1. The isthmus uteri begins to be unfolded at the beginning of pregnancy when ovum implantation takes place, to constitute the uterine portion of the lower uterine segment.

2. The upper and lower segments of the uterus manifest recognizable structural differences but their functional differences are manifested during labor.

3. The formation of the lower uterine segment is completed at the end of the first stage of labor when the cervical canal becomes completely effaced.

4. The cervical canal, during labor not only dilates, but elongates. And contrary to the prevailing view, at the end of the first stage of labor the cervix rather than the isthmus takes a larger share in the formation of the lower uterine segment.

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## LEIOMYOMA OF THE BLADDER*

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WELL-ESTABLISHED instances of leiomyoma of the bladder are rare. De Berne-Lagarde collected thirty-six cases in 1929. In 1931 Kretschmer added twelve cases and published two excellent analytical papers on the subject. We have found ten additional reports of vesicle leiomyoma, which, with the case here reported, increase the total to fifty-nine cases.

S. B., a married, nulliparous Jewish woman of thirty-six years, was admitted to the Gynecologic Service of the Hospital of the University of Pennsylvania Sept. 9, 1933.

The remote history was irrelevant.

Her principal complaints were frequency and difficulty of urination. Frequency, which was first noticed eight years previously, had gradually increased until urination was necessary every half hour. Because walking aggravated the urgency the patient became confined to her home, and during the weeks just prior to hospitalization, to her chair. For several months she had noticed a decrease in the force of the urinary stream, but the flow could be improved by suprapubic manual pressure, a maneuver which finally became essential to urination. She had a sense of incomplete emptying after voiding.

Other symptoms commonly mentioned in bladder wall tumors, incontinence, pain, and hematuria, were absent.

Physical examination revealed a well-nourished woman with no apparent distress or disease. Examination of the head, eyes, ears, nose, mouth, and throat was negative. The lungs were clear and the heart was normal. The blood pressure was 135/90. Abdominal examination was negative except that pressure on the hypogastrium excited a desire to void. The tendon reflexes were normal.

Pelvic examination disclosed normal pelvic organs. In the midline, behind the symphysis, a firm, lemon-sized mass could be felt.

The laboratory reported 4,800,000 erythrocytes, and 9,300 leucocytes per cubic millimeter of blood, 90 per cent hemoglobin (Sahli method), negative blood Wasser-

*Presented at a meeting of the Obstetrical Society of Philadelphia, May 3, 1934.

mann, blood urea nitrogen 12 mg. per 100 c.c. A catheterized specimen of urine showed abundant albumin, many clumps of leucocytes per high power microscopic field, and occasional erythrocytes. Stains for acid-fast organisms in the urine were negative.

At cystoscopic examination the cystoscope was deflected by a massive protrusion from the left median anterior wall of the bladder. The mucous membrane overlying the mass was normal. The cystoscopic diagnosis was "intrinsic tumor of the wall of the bladder" or "extravesical tumor exerting pressure against the bladder."

A urogram made with intravenous neoskiodan showed a large median filling defect of the bladder, interpreted as due to an intrinsic tumor of the bladder (Fig. 1).

Suprapubic extraperitoneal cystotomy was performed under nitrous oxide and ether anesthesia. The egg-sized tumor could be seen attached by a wide base to the anterior median portion of the bladder just above the internal urethral orifice. The overlying mucosa was incised and the tumor was shelled out with little difficulty. An indwelling urethral catheter was inserted and the bladder was closed. The space of Retzius was drained.

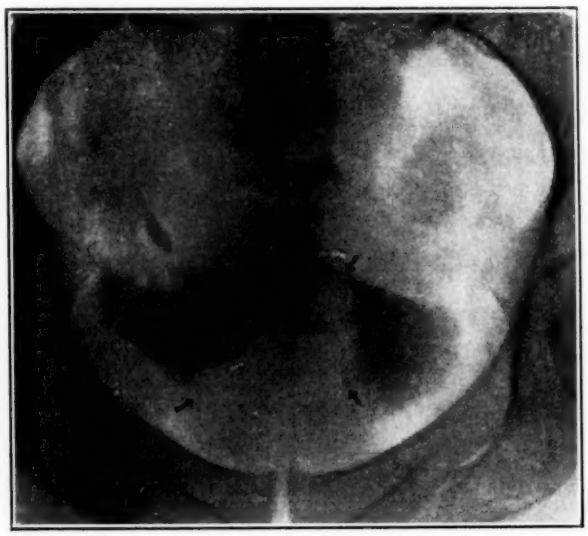

Fig. 1.—Urogram. The arrows point to the filling defect due to the vesicle myoma.

Convalescence was uneventful except for a wound infection which prolonged hospitalization. On the twenty-fifth postoperative day the patient was discharged from the hospital with no urinary symptoms. Cystoscopy revealed a healing scar of the vesicle mucosa. Six months after operation the patient reported herself entirely well and symptomless.

*Pathologic Report.*—"The tumor measures 7 by 4 by 3.5 cm. It is encapsulated and the capsule strips with difficulty. The tumor is firm in consistency and there is definite lobulation. The cut surface is grayish white in color and is moist. The appearance is that of fibrous tissue divided into lobules by distinct trabeculae. A considerable number of blood vessels give a vascular appearance to the cut surface. On sectioning the tumor there is an appearance of hyaline degeneration (Fig. 2).

"Histologically, all four sections taken from the tumor show the same general characteristics. In none is any investing epithelium present. The capsule is rather

thin and is composed of muscular tissue. The substance of the tumor is composed of irregular sized whorls between which are trabeculae of dense fibrous tissue. No muscular tissue can be identified in the substance of the tumor. The general appearance is that of a leiomyoma. Many of the cellular elements are compressed. The nuclei, for the most part, are spindle-shaped and take the hemotoxylin stain deeply. They are central in situation. No mitosis is present. The neoplasm is

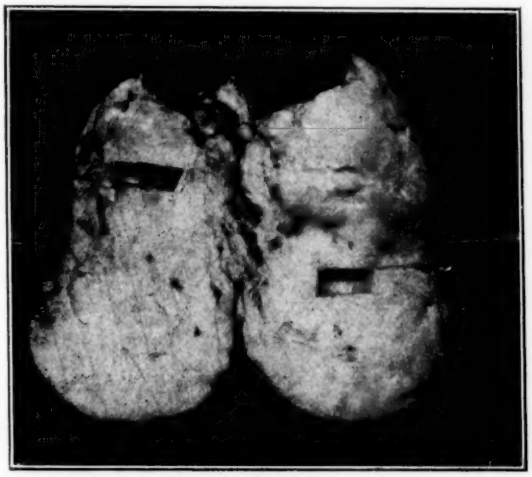

Fig. 2.—Tumor bisected and laid open.

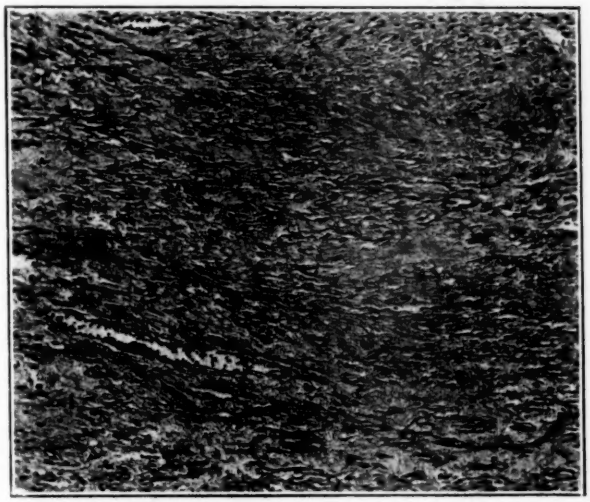

Fig. 3.—Leiomyoma of the bladder. Microscopic appearance.

moderately vascular, and apparently has a peripheral circulation. The tissue is edematous and in some areas shows definite hyaline degeneration. There is no suggestion of malignancy.'' (Fig. 3.)

After reviewing the literature on leiomyoma of the bladder these facts are apparent:

1. Leiomyoma of the bladder occurs at any age from the second to the seventy-fourth year.

2. It occurs with equal frequency in the two sexes.

3. The growth may vary in size from a microscopic nodule to a mass weighing nine kilograms, and may occur in any portion of the bladder, including the trigone.

4. The tumor may be symptomless; or hematuria, frequency, dysuria, or pain may be present.

5. Diagnosis is made by a three-step procedure: bimanual pelvic examination, cystoscopy and cystography. The most important single finding is normal mucosa covering a tumor of the bladder wall.

6. Vesicle leiomyoma may be mistaken for an extravesicle tumor distorting the bladder, for example, myoma of the cervix uteri, ovarian tumor, or prostatic enlargement.

7. Leiomyoma of the bladder is a benign tumor which manifests itself by mechanical irritation or obstruction, and which may endanger health by favoring urinary tract infection or by occluding the ureter.

8. The treatment is surgical removal.

9. The prognosis is good provided the tumor can be completely removed and provided there is no advanced renal pathology.

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NOTE: Kretschmer's list of 48 cases includes the 36 cases of Berne-Lagarde and in addition the cases of Bohme, Bouchard, Capser, Chamberlain, Gronberger, Kidd and Turnbull, Levings, McNally, Kretschmer, Scholl, Wershub, and Zuckerkandl.

133 SOUTH THIRTY-SIXTH STREET

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**Fuge, K.: Investigation of the Gastric Acidity in Women with Genital Carcinoma.** Monatschr. f. Geburtsh. u. Gynäk. **97:** 37, 1934.

In a series of 80 women who had uterine carcinoma, Fuge studied the gastric acidity according to the Ewald-Boas method. In 115 cases there was anacidity and in 25 additional cases a hypoacidity present. Most of the women in this series had inoperable cancers and had received radiation therapy. Nearly all the women had anemia. The author urges that all women with achylia be treated for this condition because disagreeable symptoms will otherwise arise. He recommends for this purpose a mixture of hydrochloric acid and pepsin.

J. P. GREENHILL.

# THE USE OF FOLLUTEIN IN DYSMENORRHEA*

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*(From the Department of Obstetrics and Gynecology of the University of Illinois)*

THERE is no need to discuss at length the physical, economic, and social effects of dysmenorrhea and the loss of time and suffering which it causes. It has been relegated to the category of minor gynecologic conditions by the medical profession, but to the individual sufferer it is of major importance. Any method of treatment which will give partial or temporary relief is gratefully received by these patients and should receive attentive consideration by the gynecologist.

Theories as to the etiology of this condition were formerly concerned with mechanical factors to a large degree, and consequently the treatment prescribed was designed to overcome these mechanical factors. As many of these patients present themselves for consideration during their early menstrual life before marriage or childbirth a fair percentage are found to have anteflexed uteri with conical closed cervices. Dilatation of the cervix with straightening of the anteflexion seemed a logical manner of correcting the supposed abnormality. There have been a sufficient number of good results both temporary and permanent following this treatment for it to have become the method of choice in many of these cases. Many others received only temporary benefit, however, after having been subjected to the trauma and expense of an operative procedure.

Others were advised that their condition must be endured with what help sedatives could afford until after marriage and childbirth when relief might be expected. The relief following childbirth with its growth and hyperplasia of the uterus as well as the dilatation of the cervix which occurs during labor, was assumed to be due to the stimulation of the uterus and the stretching of the cervix. Undoubtedly these factors played some part in the relief afforded, but the endocrine factor involved during pregnancy cannot be ignored as being without some possible benefit.

Without going into a detailed description of the mass of experimental work which has been done in recent years regarding the endocrine physiology of the pituitary and the ovary, we briefly list the presumptive functions and actions of the hormones which they produce as follows: Prolan A from the anterior lobe of the pituitary stimulates follicle ripening, while Prolan B stimulates luteinization. During follicle ripening folliculin is formed which produces growth and vascularization of

*Read at a meeting of the Chicago Gynecological Society, April 20, 1934.

the uterus and hyperplasia of the endometrium. In addition folliculin has been shown to stimulate uterine contractions. Progestin, elaborated in the last half of the menstrual cycle produces the secretory or pregravid phase of endometrial growth and in addition inhibits further follicle ripening, inhibits uterine contractions and diminishes the renal threshold for the excretion of folliculin.

During pregnancy there is an elaboration of a hormone-like substance, which in the presence of adequate pituitary tissue, will cause follicle ripening, corpora hemorrhagica and luteinization in laboratory animals. If this substance does not remain fresh, the Prolan A-like action fades and the Prolan B-like action predominates, resulting in luteinization and apparent follicle inhibition or arrest of follicle growth. Using an extract from the urine of pregnant women (antuitrin-S), Geist showed a similar effect in the ovaries of women.

In the absence of pelvic pathology and acquired stenosis of the cervix, an endocrine theory of dysmenorrhea has been hypothecated by some observers as follows: Deficient progestin formation, whether primary from insufficient Prolan B or secondary from failure of the ovary to react to its luteinizing effect might result in uninhibited action of folliculin during the premenstrual and menstrual time. This conceivably would result in folliculin stimulated uterine contractions of a painful nature and possibly menorrhagia and clots from a stationary hyperplasia of the endometrium. Another type of imbalance might result from overproduction of folliculin in the presence of an average amount of progestin. Both of these hypothetical hormone derangements might be altered by the administration of a substance which would luteinize and at the same time depress or inhibit follicle activity.

It was the above line of reasoning plus the by-effects of follutein in some cases of abnormal uterine bleeding which prompted this clinical investigation. Two women who had received follutein in an attempt to control menorrhagia reported that in addition to receiving benefit in controlling their profuse menses, that the dysmenorrhea they had previously suffered from was definitely improved. It was decided to administer follutein to a group of patients whose chief complaint was dysmenorrhea, and to survey all patients who had received this substance for other menstrual disorders who had a concomitant dysmenorrhea.

The substance used was follutein, a commercial anterior-pituitary-like substance.* In most cases the dosage administered was ½ c.c. intramuscularly daily for five days, making a total of 625 rat units. The time of the menstrual cycle at which this substance was injected was not carefully chosen at first, but subsequent experience seemed to indicate that at least two weeks should elapse from the time the injec-

*Prepared from the urine of pregnant women by E. R. Squibb & Sons Co.

tions were started until the menses began, if the maximum effects were to be obtained. Systemic and local reactions were the rule, the deltoid muscle becoming sore, the skin in many instances showing erythema and from six to ten hours after the first injection many patients were chilly, nauseated, and febrile. Subsequent injections gave less local symptoms and practically no systemic symptoms.

An attempt has been made to evaluate the tissue effects on the human ovary of this substance in three cases, using two other cases with very similar findings as controls. Two colored patients, one twenty-two and the other twenty, both married, one having had a supposed early abortion some years before, both having been previously curetted, gave a history of irregular and prolonged menstruation since the onset at puberty. An attempt was made to control the bleeding of one patient with follutein but after six weeks' amenorrhea the condition returned and a second course failed. A third course was given just prior to operation (ten days). The other patient received no treatment. Both were flowing at the time of operation at which time bilateral polycystic ovaries were found, the cysts being about navy bean size. Two cases of uncomplicated uterine fibroids with regular menstruation were treated ten days before operation and the operation performed on one, one week before the next period was expected and on the other just at the end of menstruation. The fifth patient was not injected but was also operated upon for uncomplicated fibroid uterus at the end of menstruation. The slides of the ovaries seem to show more interstitial vascularity and perifollicular and intrafollicular hemorrhage in those cases receiving follutein. The effect on the granulosa cells and the theca interna cannot be accurately evaluated from such a small number of cases but these changes conform to those described by Geist in cases treated with a similar preparation. It is impossible to determine the significance of these apparent changes.

Thirty-nine patients have been treated with follutein and reports of one month or more have been obtained. A detailed analysis of these cases individually is appended. They have been classified into three groups according to clinical types and as to whether they presented other menstrual disorders. The results have been encouraging as a number of patients in each group received substantial relief. The duration of the relief in many cases is as yet unknown as insufficient time has elapsed since treatment to determine whether the symptoms will return or whether the relief will be permanent. The group of patients with no associated menstrual disorder who were clinically feminine in type have received only one course of treatment, and those benefited have as yet had no recurrence.

No attempt was made to alter other possible etiologic factors which might augment or aggravate the dysmenorrhea. The psychic effect of

TABLE I. NO ASSOCIATED MENSTRUAL DISORDER, PERIODS REGULAR, PATIENTS CLINICALLY FEMININE IN TYPE

| NO. CASES | GOOD RESULT | FAIR RESULT | NO EFFECT |
|---|---|---|---|
| 10<br>Average duration | 5<br>3½ mo. (1-6 mo.) | 2<br>3½ mo. (2-5 mo.) | 3<br>(2 definitely neurotic) |
| Percentage | 50 | 20 | 30 |

TABLE II. CASES ASSOCIATED WITH DELAYED, IRREGULAR AND SCANTY MENSES AND PERIODS OF AMENORRHEA

| | NO. CASES | RESULT | | | RECURRENCES | REMARKS |
|---|---|---|---|---|---|---|
| | | GOOD | FAIR | NONE | | |
| Pituitary type | 7 | 5 | 2 | | 1 after 8 mo. good result | |
| Feminine type | 10 | 6 | 3 | 1 | 1 after 6, 1 after 3 mo. good | 1 case failure suspect cervical stenosis |
| Hypothyroid type | 1 | | 1 | | | |
| Total | 18 | 11 | 6 | 1 | | |
| Average duration | | 4 mo. (1 to 8) | 3½ mo. (2 to 5) | | | |
| Percentage | | 61 | 33 | 6 | | |

TABLE III. CASES ASSOCIATED WITH MENORRHAGIA AND FREQUENT MENSES

| | NO. CASES | RESULT | | NONE | RECURRENCES | REMARKS |
|---|---|---|---|---|---|---|
| | | GOOD | SLIGHT | | | |
| Feminine type | 9 | 4 | 3 | 2 | 1 good after 6 mo. and 1 after 4 mo. | 1 failure neurotic. 1 failure suspect incomplete abortion |
| Average duration | | 8 mo. (2-12) | 6 mo. (2-12) | | | |
| Percentage | | 44 | 33 | 22 | | |

these injections cannot be accurately evaluated. The first few patients were frankly told that the procedure was experimental, could do no harm, and might be beneficial. Later as the results began to appear, other patients were told that some relief might be expected. Some of these have continued through several periods with alleviation of symptoms.

Because of the encouraging results from this treatment in a fair proportion of cases the following conclusions have been drawn:

1. Certain cases of dysmenorrhea may have an endocrine basis.

2. Luteinizing substances may give partial or almost complete relief, the duration of which is as yet unknown.

3. These substances deserve a trial in the absence of pelvic pathology, particularly in patients of the feminine type where there is no associated menstrual disorder, before recourse is had to surgical procedures or irradiation therapy.

# SEXUAL EXCITABILITY AS RELATED TO THE MENSTRUAL CYCLE IN THE MONKEY

JOSEPHINE BALL, PH.D., AND CARL G. HARTMAN, PH.D., BALTIMORE, MD.
*(From Carnegie Institution)*

SEVERAL systematic attempts have been made to determine cyclic changes in the sex desire of women. The methods employed in these studies (Stopes,[1] Davis,[2] Hamilton[3]) lack the objectivity desirable in a scientific study and the results are further vitiated by the inaccuracies of memory on the part of the subjects. Moreover, the most important event in the menstrual cycle, namely ovulation, is at present not ascertainable with accuracy in women.

Inasmuch as the important events of the cycle can be readily determined in favorable female rhesus monkeys and since their sexual physiology in all essential respects seems to parallel that of women (Corner,[4] Allen,[5] Hartman[6]), this animal seemed a promising subject for studying certain aspects of sex behavior and its physiologic basis. A first step in such a study has been made by correlating quantitative changes in sex desire with the physiologic events of the menstrual cycle.

Sexual excitability was measured by recording the frequency with which certain sexual elements of the female's behavior occurred when she was mated successively to each of four different males for periods of ten minutes. The three behavioral units chosen for this measurement were: (1) "presenting"; (2) attempts to attract the male's attention by threatening an outsider; (3) going toward as against going away from the male. The first two are obviously sexual behavior and they are reacted to as such by the male. The third shows some correlation with them and was therefore considered to be an indication of sex desire.

Eight females have been studied for from three to eight months each. Tests were made three times a week. The sexes were kept segregated except during the tests.

The physiologic changes in the sex tract were followed by means of vaginal smears and rectal palpation of the uterus and ovaries.[6] In the cases here reported, therefore, the exact time of ovulation is known.

Primates differ from the lower mammals in accepting copulation throughout the cycle instead of for only a short period at the time of ovulation. The present observations indicate, however, that sexual excitability typically increases just before ovulation and falls thereafter, even though the drop is not usually so complete as to mean consistent refusal to mate.

This relationship between sex desire and ovulation is shown graphically in Fig. 1, where sex desire scores are plotted against the number of days before and after ovulation, which event is indicated by the vertical line down the center of the chart. Each curve represents one cycle, from the first observation after the beginning of menstruation to the last test before the succeeding period.

The cycles shown in this chart have been chosen from all the cycles studied as being the only ones where the behavior was obviously satisfactorily measured and ovulation was definitely determined. There were many cycles in which the animals did not ovulate, some in which ovulation was not determined with certainty, and a few in which ovulation was ascertained but behavior did not change. We cannot be sure

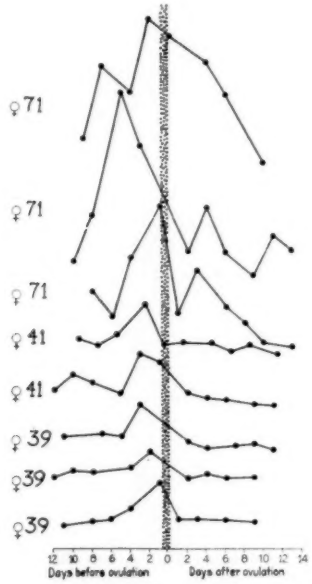


Fig. 1.—Rise and fall of sex desire in the menstrual cycle of the monkey. Six cycles, plotted from the day of ovulation.

that sex desire was measured under the most favorable circumstances in these cases. The purpose of the present paper is to report only the typical picture. Exceptions to the rule will be discussed later after more cases have been studied.

As Tinklepaugh[7] has pointed out, this rise before ovulation is what is to be expected on the basis of the relation of estrus to ovulation in those animals which have a limited mating period. He found that a pair of chimpanzees copulated only during the time of swelling of the sex skin of the female which, however, in that animal extended over the greater part of the cycle after the menstrual flow had ceased. Zuckerman[8] reports that male baboons show a preference for females with swollen sex skin and that the females in this condition stayed close to their males, presenting frequently. The swelling of the sex skin in certain primates is roughly associated with ovulation.

Comparing the curve for the monkey shown in Fig. 1 with the curves of sex desire reported for women (Stopes, Davis, Hamilton, Tinklepaugh), it is to be noted that the premenstrual rise reported for women is entirely absent in the monkeys. This fact raises the question, "Are women different or have the answers they have given investigators been about something more complex than what we have measured in the monkey?" Tinklepaugh[7] has suggested that affection is a complicating factor in the human. There may be others. We suggest that a more precise definition and an effort to analyze the factors influencing sexual excitability in women should perhaps be the next step in trying to obtain information from human subjects about the trait we have measured in monkeys. We define this trait as the amount of sex response that is elicited by a relatively constant stimulus. A similar definition that would be better suited to human conditions might be the amount of stimulation necessary to bring out a relatively constant response, such as local glandular secretion or orgasm. However, whatever definition of sexual receptivity is considered suitable, it is hoped that the objective method it has been possible to use in the study of monkeys may help to define the problem in further investigations of sex responses in women.

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**Day, Hilbert F.: Uterine Bleeding From a Needle in the Uterine Cervix,** New England J. Med. **211:** 29, 1934.

Slight uterine bleeding in a woman fifty-seven years old. Had three operative deliveries and in interval between second and third a plastic operation on cervix and perineum. On suspicion of malignancy (without preceding curettage) a vaginal hysterectomy is performed. As cause of the hemorrhage is discovered the rusty part of a surgical needle undoubtedly lost during the cervical repair but not displaced by the subsequent third delivery which had occurred twenty-two years before this hysterectomy.

Hugo Ehrenfest.

# OVARIAN RESPONSE IN MONKEYS (*MACACUS RHESUS*) TO INJECTIONS OF ANTUITRIN-S

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*(From the Department of Obstetrics and Gynecology Yale University School of Medicine)*

HISAW[6] and others have shown that subcutaneous injections of an aqueous pyridine extract of the anterior pituitary produce a marked follicular response in the ovaries. We have been able without difficulty to verify this statement with respect to *Macacus rhesus*. It has been assumed by others that similar effects would be induced by the injection of extracts of pregnancy urine. In other words, do these so-called anterior pituitary-like substances isolated from pregnancy urine produce changes in the ovary similar to those produced by extracts of the gland itself?

Engle working with rodents in 1929[3] and with monkeys in 1933[2] concluded that the changes were not similar. The work of Schockaert,[8] Evans, Meyer and Simpson,[4, 5] Leonard,[7] and Smith and Leonard[9] also substantiate this conclusion.

Recently antuitrin-S and other similar preparations have been advocated by certain clinicians as a means of controlling functional bleeding from the uterus, a control thought originally to be brought about by the stimulation of luteinization of the follicle. We were interested to learn the effect of this extract upon the ovaries of the *Macacus rhesus*, and accordingly, varying doses were administered in the following way to five mature and one immature animal:

Exploratory laparotomies were performed upon Macaques 38 and 40 weighing 5,045 and 4,935 gm., respectively, upon July 8, 1932. At this time the ovaries were measured and observations of the character of their external surfaces were recorded. Beginning July 22 and continuing until August 3, each animal received daily subcutaneous injections of 200 R. U. of antuitrin-S, until a total of 2,400 R. U. had been administered. On August 3 a second laparotomy was done, and the left ovary was removed. Serial microscopic sections of these ovaries were studied but no morphologic change in the follicles was noted.

Macaques 13 and 34, weighing 5,330 and 5,540 gm., respectively, had been in the laboratory for six months and during this time a complete menstrual record had been kept. On Aug. 6, 1932 the left ovary of each animal was excised as a control. Observations and measurements of the right ovaries were likewise made. Beginning the following day each animal received 200 R. U. of antuitrin-S subcutaneously daily for two weeks, a total dosage of 2,800 R. U. On August 20 exploratory laparotomies revealed no gross changes in the remaining ovary in either animal. The right ovary of Macaque 34 was removed for histologic study. Comparison of serial sections of this ovary with serial sections of the left ovary previously

removed as a control showed no follicular changes corresponding to those produced by the subcutaneous injection of aqueous pyridine extracts of the anterior lobe.

It was then decided to test the effect of much larger doses of antuitrin-S. M. Rh. 36 weighing 7,795 gm. and whose menstrual history had been followed for seven months was chosen as a suitable animal. Beginning Nov. 23, 1932, 450 R. U. were injected twice daily until December 5, when a total dosage of 5,400 R. U. had been given. On December 5, or fourteen days later, the uterus, both ovaries and the fallopian tubes were removed for histologic study. Aside from a very slight or questionable cystic degeneration of the follicles and the presence of fewer mitotic figures, these ovaries upon microscopic examination differed in no way from those of a so-called normal ovary.

Hisaw[6] and Diddle[1] experimenting with sexually immature female monkeys, found that following the subcutaneous injection of an aqueous pyridine extract of the anterior pituitary, the ovaries increased to eighteen times normal size and contained enlarged follicles. It was of interest therefore to determine whether corresponding changes could be produced by the subcutaneous injection of relatively large doses of antuitrin-S. For this experiment an 1,800 gm. animal, M. Rh. 31 that had been in our colony for over a year, was used.

On Nov. 4, 1932, an exploratory laparotomy was done under nembutal and ether anesthesia, and measurements of the uterus and ovaries were made. Beginning Nov. 16, 1932, 300 R. U. of antuitrin-S were injected subcutaneously at 9:00 A.M. and 5:00 P.M. daily until November 22, when a total dosage of 3,600 R.U. had been given. On that day an exploratory laparotomy showed no gross changes in the uterus or ovaries. Beginning the following day (November 23) these injections (300 R. U. antuitrin-S at 9:00 A.M. and 5:00 P.M.) were repeated daily until December 6, when a total of 10,800 R. U. had been administered. A laparotomy on this day revealed no gross changes in the ovaries or uterus. However, the right tube and ovary were removed for histologic study which proved negative.

From December 19 to and including December 27 the animal was given 150 R. U. at 9:00 A.M. and 5:00 P.M. daily. From December 28 onward, antuitrin-S was administered in the following sequence: Upon December 28 and 29 100 R. U. were given intravenously and 200 R. U. subcutaneously. Upon December 30 and 31 300 R. U. were injected directly into the heart. From January 1 to January 5 this dose was increased to 500 R. U. daily. Only a moderate reaction followed these intracardiac injections.

Upon January 6 following a total dosage of 16,500 R. U. the animal was killed. Grossly, the remaining left tube and ovary were normal and these findings were confirmed by the study of microscopic sections.

## CONCLUSIONS

1. In the case of four mature *Macacus rhesus* monkeys, the daily injection of 200 R.U. of antuitrin-S to a total dosage of from 2,400 to 2,800 R.U. produced no histologic evidence of luteinization of the follicles of the ovary.

2. The injection into a fifth mature animal of 450 R.U. daily to a total dosage of 5,400 R.U. gave correspondingly negative results.

3. The injection into an immature animal of varying doses of antuitrin-S over a period of two months, at the end of which period 16,500 R.U. had been administered, produced no microscopic evidences of luteinization of the ovarian follicles.

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## SIMULTANEOUS BILATERAL TUBAL PREGNANCY

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COMPARATIVELY few authentic cases are reported in the literature in which simultaneous bilateral tubal pregnancy occurred.

Paul Bloch cited fifty-seven cases, the first having been reported in 1890. Schochardt, reporting a case in 1928 quotes Cheval as stating that there are only sixteen authentic cases on record, while Meyer in 1931, reviewing the literature, reports twenty-eight authentic cases. F. D. Johnson reported one other case in 1932.

The case reported herein is of special interest in that:

1. The patient had no premonitory manifestations suggesting ectopic pregnancy prior to her initial attack.

2. Tubal abortion of one tube and ruptured tubal pregnancy of the other tube.

3. Histologic corroboration of the surgical findings.

Mrs. M. M. (No. 04913), white, aged thirty-eight years, was admitted to the Brooklyn Women's Hospital on Oct. 23, 1933, with a history of having experienced, eight hours previous to admission, a sudden stabbing pain in the lower abdomen accompanied with vomiting which caused her to faint. This acute pain in the abdomen had radiated to the left shoulder. She fainted four or five times after the initial attack and could not sit up in bed on account of the pain and dizziness.

Catamenia began at the age of thirteen years, every twenty-eight days, lasting four to five days, last period Aug. 12, 1933. Married thirteen years. Two normal spontaneous deliveries, twelve and nine years previously. Spontaneous abortion five years ago followed by curettage for bleeding, with no apparent sequelae.

*Physical Examination.*—Patient in shock; pulse small, thready, 140; respiration 30; temperature 100° F. The heart and lungs negative. Abdomen tense and rigid, with greatest spasticity in the R. L. Q. There was a bluish discoloration around the umbilicus (Cullen's sign).

Vaginal examination: No bleeding, cervix pointing downward, very tender to touch and on motion, fullness and bogginess in the right fornix extending posteriorly into the culdesac which was also tender to touch. The size of the uterus could not be made out on account of spasticity of the abdominal muscles. Impression at this time was that of a ruptured ectopic.

*Operation.*—Free and clotted blood was found in the abdominal cavity and posterior culdesac. Uterus enlarged and soft. Right tubal abortion with a clot ex-

tending well into the frimbriated portion. Left tubal rupture situated about one-eighth of an inch away from the cornual junction of the uterus (Fig. 1). Ovaries were small with corpus luteum of pregnancy in left ovary.

Right salpingectomy and left salpingo-oophorectomy with ventral suspension of the uterus were performed. Transfusion of 700 c.c. of Type 2 (Moss) whole blood from family donor was given at the time of operation with no immediate reaction.

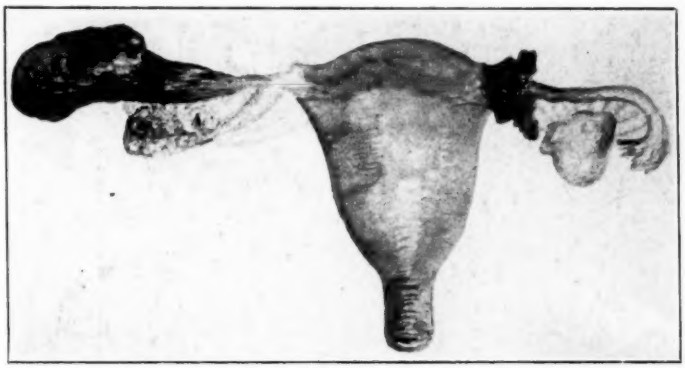

Fig. 1.

Fig. 1.—Showing tubal abortion of right tube rupture of left tube.

Fig. 2.

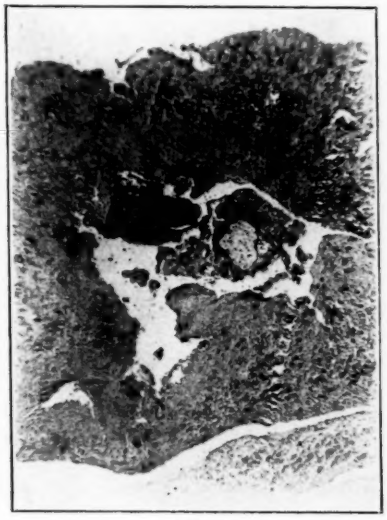

Fig. 3.

Fig. 2.—Section of the vicinity of the defect shows decidua and partly necrotic chorionic villi invading the wall of the tube.

Fig. 3.—Section of the right tube shows blood clot with chorionic remnants, indicating the abortion of the tubal pregnancy.

*Pathologic Report* (Dr. Goldzieher).—Right tube was of practically normal appearance and caliber with the exception of the terminal portion. About 2 cm. of the latter showed swelling which included the fimbriated end of the tube. The swollen portion was dark red in color, the wall was distended and the lumen filled with a massive coagulum.

The other tube was of normal appearance throughout, except for the medial portion close to the uterus. This portion showed a fairly large defect with ragged edges, while the remnants of the tubal wall were considerably thinned out. Microscopic examination of the vicinity of the defect showed decidua and partly necrotic chorionic villi invading the wall of the tube (Fig. 2).

Microscopic section of the other tube showed blood clot with a few chorionic remnants, indicating the abortion of the tubal pregnancy also in this tube (Fig. 3).

The ovary showed a definite corpus luteum of pregnancy (Fig. 4).

On the third day postoperative temperature reached 101° F., but was otherwise normal throughout. On the fourth day postoperative, respirations became very

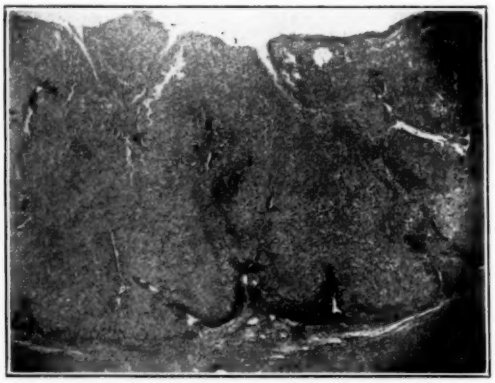

Fig. 4.—Section showing corpus luteum of pregnancy.

rapid and labored with dilated ala nasi but temperature remained low. Examination of the chest showed a massive collapse of the right lung. This responded very readily to treatment of $CO_2$ and O.

The patient was discharged on the fourteenth day, with the following note: wound healed by primary union. Temperature, pulse, and respiration normal. Blood pressure 118/70. All signs in chest clear. No vaginal bleeding.

On Dec. 21, 1933, abdominal scar was firm. Patient menstruated on December 7 for three days, no clots. Vaginal examination showed the cervix in the axis of the vagina. Uterus anterior. No pelvic tendernesses or masses palpated. Chest clear. Blood pressure 140/92. Hg, 80 per cent.

536 Saratoga Avenue

# LOCALIZED TRAUMATIC CYANOSIS IN THE NEWBORN

J. H. Telfair, M.D., and J. A. Gaines, M.D., New York, N. Y.
*(From the Department of Obstetrics, Fordham Hospital)*

TRAUMATIC cyanosis is a relatively rare entity. There are approximately 143 reported cases, which moreover, as far as we have been able to ascertain, do not include a single occurrence in the newborn. The condition per se is extremely spectacular and has made an indelible impression on the minds of those who have had the opportunity to view this picture following the crushing trauma of machine, vehicle or panic-driven mob. We submit the report of a case with necropsy findings, in which this phenomenon resulted as a complication of labor. We shall first present, however, a review of the salient features of traumatic asphyxia or cyanosis with special reference to its pathogenesis.

Traumatic asphyxia refers to a localized, deep cyanosis of the face and neck which immediately follows a sudden compressing force exerted upon the thorax or abdomen. The picture is striking not only because of its unusual distribution but also because of the characteristic discoloration which is livid blue, purple, or blue black. Minute ecchymotic spots or petechial hemorrhages are usually present. The discoloration begins to fade in two to four days and often disappears within two to three weeks, without, however, the color exhibiting the changes of tint usually seen following subcutaneous hemorrhages. The area of involvement is not always confined to the face and neck. Sometimes it extends as far as the third rib anteriorly and posteriorly along the shoulders to the lower level of the trapezius muscles. The reported cases followed for the most part a crushing injury in panics or direct compression by machines. The force need only be exerted for a few seconds to a few minutes, and often except for abrasions and contusions have not caused any apparent injury of the chest wall, lungs, heart, or mediastinal structures. Of course from the nature of the etiology there may be concomitant and sometimes fatal injuries, but the majority of reported cases recovered, and those that did not succumbed apparently to the more serious associated injuries.

Perhaps the nearest approach to the case to be reported is that described by Kredel.[1] "An infant only seventeen hours old presented an umbilical hernia containing the whole liver and the greater part of the intestines. Great pressure had to be exerted upon the liver to reduce it into the abdominal cavity and great force was necessary to close the abdominal wall. At the end of the operation, the child's face showed a deep blue discoloration marked by numerous petechial hemorrhages. It was his opinion that the pressure exerted upon the liver caused a large mass of blood to flow into the right heart and that this pressure was communicated to the face and neck."

*Case Report.*—On the twenty-first of December, 1933, Mrs. L. D., thirty-seven years of age, gravida x, para vii, gave birth to a nine-pound twelve-ounce male infant. Her pregnancy had been uneventful except for a moderate hypertension and albuminuria on admission. The entire labor lasted for seven hours. The second stage was estimated at forty-five minutes. The labor pains at the time of delivery were extremely weak. Delivery of the head required the aid of Kristellar expression. There was some difficulty and delay in delivering the shoulders.

[1]*Kredel:* Zentralbl. f. Chir. 34: 1472, 1907.

At birth the infant showed marked finely mottled, purple cyanosis of the face and neck and moderate cyanosis of the extremities. Though there was no evidence of vaginal or perineal laceration, bright red blood was aspirated from the pharynx. A small amount was also expressed from the nose. The cry was weak. The cyanosis of the hands and feet disappeared but that of the face remained a deep purple blue with numerous small petechial hemorrhages. The conspicuous contrast between this unusual localized and demarcated discoloration of the face and the rest of the body simulated in every way the colorful pictures of traumatic cyanosis seen in adults. Soon the usual indications of cerebral hemorrhage made their appearance including general apathy, weak, high-pitched cry, feeding difficulty, increased respiration and bloody spinal tap. Irregularly at first and more persistently near terminus, the extremities also showed moderate cyanosis, *but the following observation showed not only that this cyanosis was part of the cerebral picture and entirely distinct from the traumatic cyanosis of face and neck, but also that cyanosis can be caused, on the one hand, by a decrease in oxygen content of the blood, and on the other hand, by persistent venous dilatation. When $CO_2$ (7 per cent) and $O_2$ (93 per cent) was administered to the infant the entire body assumed a rosy hue but the head and neck remained as purple as it had ever appeared before.* The child lived for a few days. Postmortem examination, performed by Dr. Louis Ferrara, showed no injury to the thoracic or abdominal organs. The right heart seemed slightly more enlarged than normal. There were no congenital cardiac abnormalities. The lungs were not atelectatic. The thymus was not abnormally enlarged and there was no occlusion or pressure upon the innominate or internal jugular veins. The veins of the neck were dilated. Examination of the brain showed slight cerebral congestion, a subtentorial hemorrhage and a dilated right-lateral ventricle. Section of the skin of the face revealed dilatation and engorgement of the vessels but no extravasation of blood into the skin.

### CONCLUSIONS

We present this case as the first instance of traumatic cyanosis in the newborn to be reported as far as our investigations have permitted us to discover. We believe that the compression encountered in the delivery of a ten-pound baby aggravated by dystocia due to shoulders was the causal factor.

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## SEPTICEMIA IN THE NEWBORN*

WALTER B. MOUNT, A.B., M.D., F.A.C.S., MONTCLAIR, N. J.
*(From the Department of Obstetrics, Mountainside Hospital)*

THE patient's first pregnancy terminated in the birth of a normal child eight years previously. In this second pregnancy there was no evidence of toxemia and the gain in weight was less than twenty pounds. Three weeks before delivery the mother received a slight injury of the abdomen which caused very little pain and of which she thought no more at the time.

Delivery at term occurred on Feb. 7, 1933, in Mountainside Hospital and was spontaneous, labor lasting less than twelve hours. The membranes ruptured in the second stage. Because of uterine inertia late in the second stage one minim of pituitrin was administered with good results. A deep median perineotomy was done, so that the baby's head was not subjected to long pressure on the perineum. The

*Presented at a meeting of the New York Obstetrical Society, May 8, 1934.

baby weighed 7 pounds and 14 ounces and was clinically normal. For a number of days after birth there were a few transitory skin lesions which were not noteworthy. He nursed well. The initial loss of weight was 9 ounces and then he began to gain slowly. On the eighth day he was circumcised; four sutures of 00 plain catgut were used, and the wound healed with no evidence of infection. On the eleventh day he weighed 7 pounds and 7½ ounces and seemed well in every way; the cord stump was clean and dry but had not dropped off; the circumcision wound was healing. He was allowed to go home with the mother. On that day the nurse developed a coryza and wore a mask over mouth and nose whenever handling the baby.

Early on the twelfth day it was noticed that the left arm moved not as freely as the right. That afternoon there developed a fusiform swelling of the left upper extremity with its midpoint slightly above the elbow. There was redness of the skin, local heat, pain when the arm was touched or moved, and a petechial spot the size of a pinhead on the anterior surface of the elbow. The left axillary glands were enlarged. There was a slight rise of temperature. The baby had a very good day and slept most of the time except when nursing. Wet dressings were applied to the arm. During the night the baby was somewhat wakeful and restless and there was a transitory strabismus.

By morning the swelling had increased. A blood examination showed no anemia, 8,400 leucocytes and 89 per cent polymorphonuclears. The urine had a faint trace of glucose and a marked trace of albumin (4-plus). A blood culture was taken. During this day, the thirteenth, he nursed very well until three o'clock. By that time the liver had definitely increased in size, the swelling and induration of the arm extended to the shoulder and the axillary glands were larger. There was some abdominal distention, and a number of small green stools and some gas were passed. Ten cubic centimeters of the mother's blood was given intramuscularly. Later there was vomiting several times of small amounts of clear fluid. The abdomen became markedly distended. The general condition and color grew worse. There was a constant grunting respiration. There was no bulging of the fontanel, no rigidity of spine or extremities, and no increase of deep tendon reflexes. There was no jaundice. There was very slight fever.

A surgeon saw the patient with the pediatrician. The peritoneal cavity was aspirated and clear, thin, yellow fluid obtained. Two incisions were made over the upper and outer part of the arm where fluctuation seemed greatest, but no pus was evacuated. The baby grew worse rapidly. He was readmitted to the hospital, and was given glucose intramuscularly, abdominal stupes, minim doses of pituitrin, a colon irrigation and carbon dioxide in oxygen. He grew weaker and died forty-five hours after the first symptom had been noticed.

The mother remained well.

Autopsy report: No eruptions. Heart, gastrointestinal tract, kidneys, brain, and meninges normal. Several dark red consolidated areas scattered throughout both lungs; stage of red hepatization. Peritoneal cavity contained considerable clear yellow fluid. Liver dark in color, enlarged and engorged with blood. Spleen somewhat enlarged and congested. Two incised wounds of upper outer part of left arm. Region of left elbow and arm swollen and the skin over this area dark red. The region of the left elbow was opened by a linear incision. When the deeper tissues were reached considerable creamy yellow pus escaped from an abscess cavity which communicated with the elbow joint and extended upward about 2 inches. The lower end of the humerus showed roughening with destruction of cartilage. Circumcision healed. Section through umbilicus showed no evidence of infection or thrombus formation. Culture from peritoneal fluid aspirated before death developed no growth. Blood culture positive for hemolytic staphylococcus.

Pathologic diagnosis: *Staphylococcus (hemolytic) septicemia.* Bronchopneumonia. Contributory cause of death: Abscess of left elbow joint and adjacent soft parts.

Only 69 cases of proved septicemia in the newborn have been reported. Of these Dunham[1] had 39 cases in a five-year period in one hospital; some of these cases were recognized only because blood cultures made during life or taken from the heart blood immediately after death were routine in all cases of unexplained illness in the newborn. Since Dunham's excellent paper with bibliography appeared early in 1933 four cases[2, 3, 4, 5] have been published, but Dr. Dunham[6] reports that there have been twelve additional cases on the Pediatric Service of the New Haven Hospital. In a five-year period there were over 3,000 births in that hospital with an incidence of eight cases of proved septicemia, the other 31 patients having been delivered elsewhere. In Dunham's 39 cases osteomyelitis occurred four times.

As obstetricians we are interested in the newborn, even though we may give to the pediatricians the entire responsibility for their welfare. This case is reported so that we shall have blood cultures taken in obscure or serious illnesses in the newborn. When *Staphylococcus albus* is reported, repeated cultures should be taken because it is a frequent contaminant. Ultimately more helpful knowledge may result. In treatment repeated blood transfusions should be used.

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# ENDOMETRIOSIS, CHRONIC BARTHOLINITIS, AND OVARIAN CYST*

CHARLES EDWIN GALLOWAY, M.D., EVANSTON, ILL.

THE patient, Mrs. C. R., a widow, aged twenty-nine years, presented the following history: Two labors, both full-term and normal deliveries in 1923 and 1924. Pelvic laparotomy nine years ago at Cook County Hospital, apparently for salpingitis and both tubes and one ovary were removed. Several Bartholin abscesses required incision and drainage. Following the laparotomy the incision did not heal properly and the patient states that from then on for six years at each menstrual period, bleeding took place from the small raised area, which now resembles a mulberry, in the middle of the incision. She also states that there has been considerable pain in the abdominal wall with each menstrual period. For the past three years, however, she has been free of the bleeding from the abdominal wound but the pain has persisted and is quite severe. It starts a day or two preceding the period and lasts a day or two after the period is over. Her chief complaint at the present time is lower abdominal pain which is almost constant. She denies having any fever.

Examination revealed a small mulberry-sized mass half-way between the pubis and the umbilicus, and underneath this was a mass approximately 5 cm. in diameter, very hard and very tender which seemed to be connected with the body of the uterus.

*Presented at a meeting of the Chicago Gynecological Society, May 18, 1934.

The vagina was normal except for a scar on either side corresponding to the location of the Bartholin gland. The cervix was not eroded. The vagina was filled with a purulent discharge. The uterus was held firmly against the abdominal wall, with a soft cystic mass to the right and posterior. Nothing could be palpated on the left side.

The Wassermann and Kahn tests were both negative; temperature normal over a period of thirty-six hours that the patient was observed prior to operation; white blood cells 17,500.

Diagnosis: Endometriosis; chronic Bartholinitis; probable ovarian cyst.

Operation: May 17, 1934. Drop ether anesthesia. A midline incision was made from the pubis to the umbilicus, including the old incision. The mass described in the anterior abdominal wall was found as expected, adherent to the body of the uterus. The same process had also extended toward the bladder. The left ovary and tube were absent and the right tube was absent. The right ovary was about the size of a lemon and was entirely cystic.

The omentum was adherent to the abdominal wall and to the pelvic viscera. With slow dissection the entire pelvic contents were freed and the right ovary together with the fundus of the uterus and the mass described, still adherent to the anterior abdominal wall, were removed intact.

The raw surfaces were then peritonealized with No. 2 plain catgut and the abdomen was closed in the usual manner using four black silk stay sutures. Before leaving the operating table the patient was given a quart of normal salt solution at 110° per rectum.

On Dec. 17, 1934, the patient was well, the incision showed no evidence of endometrial deposits, and there were no pelvic symptoms.

### PATHOLOGIST'S REPORT

Microscopic sections taken from the firm mass just beneath the skin surface showed the following: In one area small tubule and duct-like structures composed of columnar epithelium and surrounded by masses of small, dark spindle-shaped cells and lymphocytes, were scattered unevenly through the mass of coarse, dense, fibrous, connective tissue. Some of the tubules were dilated to form cyst-like structures and contained red blood cells and lymphocytes. Several of these epithelial structures with their dense cellular stroma had a striking resemblance to fundic endometrium. Another part of this tumor mass consisted of atrophic ovarian tissue. Its stroma contained a small mass of atypical epithelial elements embedded in a stroma which was more cellular than the ovarian stroma elsewhere. Imperfect alveolar and tubular structures were formed by the epithelial elements but, while these were greatly distorted, definite evidence of anaplasia was lacking.

*Diagnosis:* Endometrioma of the abdominal wall. Unilocular serous cystoma of one ovary. Chronic fibrous perimetritis and perioophoritis.

## A DEVICE FOR RUPTURING MEMBRANES

DAVID A. BICKEL, M.D., SOUTH BEND, IND.

IF AN attempt is made to rupture the membranes with an ordinary uterine forceps or other pointed instrument considerable difficulty is frequently experienced, especially if the cervix is undilated. A very convenient instrument for this purpose can be made from a discarded dilating uterine irrigator. The original instrument consists of a tubular shaft curved so that it can be easily inserted into the cervical canal. This curved shaft carries two spring steel wires attached to a screw adjustment and soldered just back of the tip (*A*). To convert this instrument into a useful device for rupturing membranes, the ends of the wires may be freed by melting the solder just back of the tip, and by means of a dental drill two small holes, through which the wires will pass, are drilled in the tip (*A*). The ends of the wires are

ground to blunt points to prevent injury to the scalp or cervix. By the screw adjustment the points of the wires may be extended beyond the tip or retracted. By marking the shaft at (*B*), near the screw adjustment, the position of the points can be determined.

Before the instrument is introduced the points are retracted to prevent injury to the cervix. After it is introduced, the points are extended about 2 mm. beyond the tip, by turning the screw adjustment. The points being rounded and not rigidly fixed to the instrument, injury to the scalp is impossible with reasonably careful technic.

515 ODD FELLOWS BUILDING

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**Keller, R.: Operation in Serious Cases of Utero-Adnexal Tuberculosis,** Bull. de la Soc. d'obst de la gynée., p. 90, January, 1934.

Keller believes that for cases of uteroadnexal tuberculosis, operation possesses many advantages. It permits the evacuation of pus. If not all, as much as possible of the tuberculous area should be taken out without fear of injuring the intestines.

Contraindications to operation exist when in addition to pelvic tuberculosis there is extensive involvement of abdominal organs or tuberculosis of distant organs or if the patient's general condition is too grave to permit an operation.

At the time of operation we should be as radical as possible. An incomplete operation will necessitate another and usually a more serious one.

J. P. GREENHILL.

# Society Transactions

## NEW YORK OBSTETRICAL SOCIETY

*MEETING OF MAY 8, 1934*

The following case reports and papers were presented:

**Septicemia in the Newborn.** Dr. Walter B. Mount. (See page 126.)

**Carcinosarcoma of the Uterus.** Dr. James A. Corscaden.

**The Fetal Mortality in the Different Types of Toxemia.** Dr. Alvin J. B. Tillman (by invitation) and Dr. Benjamin P. Watson. (See page 19.)

**Breech Deliveries. (Motion Pictures.) (1) Normal, With Repair of Laceration. (2) Breech Extraction With Repair of Episiotomy.** Dr. Hervey C. Williamson.

## OBSTETRICAL SOCIETY OF PHILADELPHIA

*MEETING OF MAY 3, 1934*

The following papers and discussions were presented:

**President's Address.** Dr. C. B. Lull.

**The Value of Irradiation in the Treatment of Ovarian Carcinoma.** Dr. J. H. Harris and Dr. F. L. Payne. (See page 88.)

**Leiomyoma of the Bladder.** Dr. F. E. Keene and Dr. P. Thompkins. (See page 109.)

**A Pharmacologic Study of the Uterine Fistula of the Unanesthetized Rabbit. I. Pituitrin.** Dr. G. L. Weinstein and Dr. M. H. Friedman. (See page 93.)

## BROOKLYN GYNECOLOGICAL SOCIETY

*MEETING OF APRIL 6, 1934*

The following papers were presented:

**Embryonal Carcinoma of the Ovary.** Drs. S. A. Wolfe and S. Kaminester. (For original article see page 71.)

**The Male Factor in Sterility.** Dr. Wm. H. Cary.

## CHICAGO GYNECOLOGICAL SOCIETY

*MEETING OF APRIL 20, 1934*

The following papers and discussions were presented:

**Hormones in Relation to Reproduction.** Dr. Carl R. Moore. (See page 1.)

**The Use of Follutein in Dysmenorrhea.** Dr. W. H. Browne. (See page 113.)

## CHICAGO GYNECOLOGICAL SOCIETY

*MEETING OF MAY 18, 1934*

The following case reports and papers were presented:

**Endometriosis, Chronic Bartholinitis, and Ovarian Cyst.** Dr. C. E. Galloway. (See page 128.)

**The Management of Pregnant Women With Heart Disease.** Dr. J. E. Fitzgerald. (See page 53.)

**Labor in the Cardiac Patient.** Dr. R. A. Reis and Dr. L. E. Frankenthal, Jr. (See page 44.)

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# American Gynecological Society

## Fifty-Ninth Annual Meeting

*White Sulphur Springs, W. Va., May 21, 22, 23, 1934*

*(Continued from December issue.)*

9. **Blood Chemistry in Preeclampsia and Eclampsia.** Drs. H. J. Stander, and J. F. Cadden, New York City. (See page 856, December, 1934, issue.)

### DISCUSSION

DR. PAUL TITUS, PITTSBURGH, PA.—This paper attempts to correlate general blood chemistry findings with treatment in eclamptic toxemia. Obviously the idea of repeated analyses by which changes may be an index of the progress of the disease, is a practical one in which the laboratory can actively assist the clinician.

I agree that preeclampsia and eclampsia is the same disease, with the mere addition in the latter of a single spectacular symptom—the convulsion, but also that *all* toxemias of pregnancy are etiologically and clinically related. There is considerable evidence to support this view.

Dr. Stander has done something quite new in his analysis and evaluation of glutathione and thioneine values. The functions of these compounds are obscure and while his results were negative, it is well that this fact has been settled. Messer of the Oliver Research Laboratory in Pittsburgh believes, however, that it is a mistake to name these nonfermenting "blood sugar" fractions "saccharoids" because they are not sugar-like but are sulphur compounds.

Stander makes a useful clinical application of progressive changes in the $CO_2$-combining power, and the blood uric acid namely, that a continued low level, or a decline in $CO_2$-combining power, with a steady increase in blood uric acid warrants active therapeutic treatment and surgical interference. The significance of uric acid increase may be speculative without impairing the therapeutic importance of this observation.

This paper finds us still somewhat in disagreement in blood sugar findings, not so much in fact as in viewpoint. He still sees only the hyperglycemia which follows a convulsion as the outstanding feature, whereas I maintain that this is merely the physiologic response to any sudden muscular activity. I find much more of significance in the peculiar low values that Stander and I and many others have seen repeatedly. It is not surprising that many eclamptic patients show high sugar values, because of the repeated muscular upheavals, but it is surprising that any

of them could be found so low as many have reported. This phenomenon, to my mind, is the one of real significance. Low levels are especially common in pre-eclampsia where the convulsion has not yet disturbed the values.

In order to explain, if possible, these peculiarly low levels seen so frequently in eclampsia, I took prolonged series of blood sugar readings at five- to ten-minute intervals in 19 eclamptics and found striking and sudden fluctuations in the blood sugar with the convulsions almost invariably preceded by a sharp fall similar to that of insulin overdosage. The actual level of the blood sugar, when this occurred, might be below, or within, or above normal values, but in relation to what it was a moment before that, or even for several readings before, it represented a sharp fall so that I coined for this the term "relative hypoglycemia." John of Cleveland has reported comparable insulin reactions and shock in diabetics with blood sugar above 200 mg., but relatively hypoglycemic when compared with the level just before the overdose of insulin was given.

I feel sure that Stander's inability to find these fluctuations and the relative hypoglycemia which precedes the convulsion with the physiologic relative hyperglycemia after them is due merely to his not having taken, in any one of his case reports which I have examined, a long enough series of readings at short enough intervals. This is particularly likely to be the answer because Laferty and his coworkers of Philadelphia as well as Siegel and Wylie of Baltimore, have repeated my studies and confirmed these findings.

After all, since these findings merely give, as yet at least, another rational basis for the use of intravenous glucose injections in preeclamptic and eclamptic patients, our partial disagreement on this does not particularly matter. Our views on treatment are the same and Dr. Stander has emphasized today, as he has before, the important relationship that should exist between the laboratory and the clinical divisions in the successful treatment of pregnancy toxemia.

DR. FRED L. ADAIR, CHICAGO, ILL.—For many years I have contended that we could not prevent or cure eclampsia by prenatal care. All we accomplish is to reduce the incidence of convulsive and comatose cases and correspondingly increase the number of preeclamptic cases.

I desire to call attention again to a group of cases which vary from the eclamptic and nephritic type. This is the hypertensive group. Essential hypertension is a vascular disorder of unknown etiology which occurs in nonpregnant women and is definitely aggravated, both temporarily and permanently, by pregnancy, and eventually results in morphologic vascular changes involving the vessels of the kidneys as well as those of other organs.

I am informed that the methods of estimating uric acid, glutathione and thioneine are not sufficiently specific and quantitatively accurate to enable one to interpret the findings in terms of disturbed metabolism and I should like to ask Dr. Stander why he associates high uric acid values with a damaged liver inasmuch as uric acid is supposed to be formed in the liver? Is the uric acid excretion increased in these cases? Is there rapid uric acid formation possibly from synthesis of fetal nucleoproteins? Is it possibly due to a starvation acidosis?

All of the chemical work done on these cases in our clinic has been carried out under the supervision of Dr. W. J. Dieckmann. The actual and relative findings are practically the same as those of Dr. Stander. It has been found that the eclamptic group shows a relatively high nonprotein nitrogen value antepartum with a rapid decrease within forty-eight hours postpartum. The values are relatively less than the normal nonprotein nitrogen ratio but show a corresponding fluctuation. This points more to a functional disturbance than to a real organic kidney lesion.

The urie acid values are also high in our series of something over fifty eclamptic and fifty preeclamptic cases. The exact significance of this is a little uncertain. It may result from alterations in diet, starvation and any functional or organic impairment.

DR. JAMES R. McCORD, ATLANTA, GA.—In 1928 in our clinic we started treating our eclamptic patients with nothing but magnesium sulphate and glucose. Our total mortality in 115 cases has been 5.2 per cent. In our last 49 cases we have lost but one woman. We have had two cesarean sections; we have done ten forceps operations and two breach extractions.

10. **A Roentgenologic Study of the Mechanism of Engagement of the Fetal Head.** Drs. William E. Caldwell, Howard C. Moloy and D. Anthony D'Esopo, New York City (Paper presented by Dr. Moloy). (See page 824, December, 1934, issue.)

DISCUSSION

DR. L. A. CALKINS, KANSAS CITY, MO.—This classification of pelves may prove to be very valuable from two points of view.

In the first place, our teaching is apparently based on a large number of unrelated abstract entities, whereas we could present most of these conditions as biologic variants. Such a presentation would have the distinct advantage of relating all of these conditions one to the other and, in the case of female pelves, would merely show variation in one direction or the other from what we regard as the strictly normal. We have known for a long time that the whole pelvic girdle, and more particularly the sacrum and coccyx, is subject to a tremendous developmental variation. This variation is not only present in regard to centers of ossification but is also manifested in marked differences in rate of growth and in angulation. These variations are rarely present in the rest of the vertebral column but are really quite striking in the sacrum and coccyx.

The phylogenetic reduction of the sacrocaudal vertebrae in the high primates has long been recognized. We should, therefore, expect not only high assimilation and low assimilation pelves but also the anthropoid type, and possibly also the android type as well. One cannot help but wonder whether the proportion of android pelves will not increase in the future. I am thoroughly convinced, after a few years' trial of this teaching method, that the student will grasp the whole picture much more readily and understand the individual types of pelves much more thoroughly.

The second point of view of importance to be attached to this work is the increased ability to prognosticate the probable "parturitional" effect of the particular size and shape of the pelvis in the individual patient. Apparently the authors have been able, in the two hundred cases studied, to better foresee the probable course of labor than by previous methods. I think we shall all be very much interested in knowing whether the experience of a larger series of cases will substantiate the findings in this comparatively small group. There is some question in my mind whether the method is perhaps not too cumbersome for general use. Certainly one could not employ it as a routine in all cases and, quite as certainly, one must have a considerable experience with it before he would be able to rely upon his judgment in reading the plates.

I have real evidence that the head enters the pelvis in the transverse diameter. I cannot help but wonder, however, whether a teaching is sound when it suggests that internal pelvic measurement is no longer necessary, as the average practitioner cannot use this more cumbersome and detailed, although perhaps far superior, method of study here recommended. Moreover, the knowledge that after careful pelvic

measurements the pelvis is essentially normal allows the attendant to direct his attention to other important factors such as the resistance of the soft parts, and the effectiveness of the labor pains, either of which is more often sufficiently abnormal to produce delay and perhaps pathology than the bony pelvis.

DR. WILLIAM E. CALDWELL, NEW YORK CITY.—We have been surprised at the ease with which two films of the fetus and the pelvis can be taken between pains. When viewed with the precision stereoscope, Varney's description of the engagement of the head has been proved as the most common method in this series of cases.

Another important point which we had not recognized before is the position of the child's body to the plane of the inlet. Normally the child's body lies in the curve of the uterus at the transverse diameter, possibly slightly anterior or slightly posterior. Even before the membranes have ruptured the body is straightened out, but even in prolonged labor the axis of the uterine forces strike the plane of the inlet at an angle instead of straight up and down, as we were led to believe. In the majority of cases the contraction of the uterus in itself brings that forward since that is the point of least resistance.

I believe that this method will save a great many cesarean sections if it is done before the uterus is contracted. In five of these cases the child's head did not rotate into the anterior posterior diameter and cesarean section was done. It seems to me that Williams was right when he said, "In a difficult situation, with a good surgeon and under proper conditions, cesarean section is frequently the easiest way out, but that is not obstetrics." I believe the x-ray films will make it necessary to do fewer cesarean sections and will make labor much easier.

DR. BENJAMIN P. WATSON, NEW YORK, N. Y.—This method of x-ray examination of the pelvis is extremely simple. It can be done in labor between pains, and when those films are viewed through the special stereoscope the information obtained is extraordinary. One can see if there is any disproportion, and how the head is entering the pelvis. Dr. Caldwell and Dr. Moloy have become so expert that they can prognosticate exactly how the head is going to go through the pelvis, and whether anterior or posterior rotation is going to occur. I know of nothing that has given us more satisfaction during the past year than has this method. It has probably saved many cesarean sections. On the other hand, it has enabled us to do cesarean section at the time of election where otherwise from the mere pelvic measurements one would say that certainly a trial labor was indicated.

**11. Circumcrescent and Circumvallate Placentas.** Dr. James R. Goodall, Montreal, Canada. (See page 707, November, 1934, issue.)

DISCUSSION

DR. PHILIP F. WILLIAMS, PHILADELPHIA, PA.—It is evident that in the earlier studies of the condition there has been lost the significance of the correlation between the clinical history of the pregnancy and the production of this alteration in the structure and shape of the placenta. Dr. Goodall regards the circumcrescence, either the concentric or eccentric type, as a physiologic effort on the part of the villi to preserve the life of the fetus. Holland and Ballantyne mentioned this condition as a cause of stillbirth, and yet from what Dr. Goodall has said I should think that if we made a further study of stillbirths or prematures, and this hypertrophy, we might find a considerable amount of interwoven evidence, that the clinical history of the woman and the pathology of the placenta were related in the premature birth or stillbirth of the child.

It is rather difficult for me to consider that the placenta could become as senile as Dr. Goodall considers it to be toward the end of pregnancy, beginning at the seventh month and working on. The last two months is the period for the greatest need of nutrition and support of the child, and if this compensatory hypertrophy is manifested in the villi, it would seem that the placenta should not become as aged as he seems to feel that it is at the time of birth.

I have seen three cases of erythroblastosis fetalis which Dr. Goodall mentioned. This was characterized by an intense anemia of the child at birth and the placenta was extremely pale, very light pink, and showed evidence of edema.

DR. OTTO H. SCHWARZ, ST. LOUIS, MO.—Williams, in a study of 30 cases of placenta circumvallata going over his clinical histories, concluded that this abnormality was practically without clinical significance.

Dr. Hobbs of my service, with a few cases fresh in mind where there were severe clinical complications, began an investigation of our material. He pointed out that in the cases studied by Williams, the patients were near term. Hobbs divided his cases into two groups, those in which the fetuses were stillborn or died soon after birth, and those in which the babies were born alive.

In the first group the circumvallata was complete in 25, and partial in 9; in the second group it was complete in 26 and partial in 19. In the first group there were 26 stillbirths with eight other deaths where the babies had lived but a few hours. The average weight of each child was 1,000 gm. In the second group, there were 45 living children all weighing over 2,500 gm. This would seem to indicate that if the lesion developed early in the pregnancy, if it did not cause definite damage to the fetus by the time of viability, the condition is of little clinical significance, but that early in pregnancy a certain definite percentage of fetuses are lost due to the presence of this lesion.

DR. CAREY CULBERTSON, CHICAGO, ILL.—The adjustment or adaptation between the growing uterus and the growing egg has been taken for granted. I feel that this is not always the case, and therefore, after the placental plate is established, this further elaboration of the frondosum results in hypertrophy, a phase which strikes me as being very adaptable to the situation. The term "circumcrescence" is one which explains that and is very well used in describing the condition.

In a series of cesarean sections we have occasionally seen a circumvallate placenta and in every case the point of imbedding was in the horn of the uterus. Theoretically the imbedding of the egg in the horn of the uterus should give us this failure of adjustment between the growing egg and the growing uterus.

DR. GOODALL (closing).—Circumcrescence is not an effort on the part of the child to preserve its life. I have observed several placentas in which the whole circumference of the placenta had undergone infarction to such a degree that function was absolutely impossible in that rim and the center of the placenta had hypertrophied to a tremendous thickness, 6 cm. in some instances. Further study showed to my surprise, that the child was living on 25 per cent of its placenta. The reserve in the fetus, in the liver, in the heart, or any of the organs, is believed by physiologists to be at least 60 per cent.

As to the question of placental senility coming on before the fetus has reached its full growth, that is a problem which it is difficult to analyze. When I first put out my work on the uterine arteries, showing that degeneration in the walls of the uterus began a few days after the puerperium began, that work had not been confirmed very long before a worker wrote and said that degeneration begins before the birth of the child. A rather startling statement and yet, perfectly true since whenever the placenta has undergone infarction a triangle is formed through the

uterine wall and that wall ceases to grow. Not only is the placenta affected but the uterine wall that feeds it undergoes degeneration also.

In this work I have tried to adopt a plan which would not interfere or bring in any preconceived ideas. In the first 500 placentas that went through I purposely ignored the histories. In the second 500 I have on the sheet not only the finding of the placenta but the clinical history also. One can deduct exactly when the first sclerosis of the placenta occurred and which is the beginning of a compensatory hypertrophy.

12. **The Management of Occiput Posterior.** Dr. William C. Danforth, Evanston, Ill. (See page 756, November, 1934, issue.)

DISCUSSION

DR. ALFRED C. BECK, BROOKLYN, N. Y.—The author's excellent results warrant a very careful study of his routine procedures. First of all, he stresses the importance of conserving the patient's strength in the first stage. To accomplish this he recommends rest and the relief from pain. We believe that food is equally important, and we insist that our patients take ample carbohydrates, particularly in the early part of the first stage. With Dr. Danforth, we are also of the opinion that the proper management of posterior positions should begin in the first stage. We also feel that the difficulties in the second stage are proportionate to the neglect in the first stage. His high incidence of anterior rotation is in accord with our experience. Dr. Danforth attributes it to his early diagnosis. I do not think that is the whole truth. I believe that his large number of anterior rotations is due to his careful conduct of the first stage.

In the second stage an abdominal binder increases the force of the voluntary efforts, and we have found that it is very valuable in aiding rotation. Dr. Danforth awaits spontaneous rotation but he also recommends interference at the expiration of two hours. That is sound conservatism for it allows nature to do her work when she can, and when she is incompetent he recommends interference at a time when interference can be done easily, before moulding of the uterus and retraction ring dystocia increases the difficulty. His high incidence of successful manual rotations prove this point as well as his maneuver. With Dr. Danforth we also recommend the avoidance of forceps rotation because of the great injury that results from this procedure in the hands of those who are not expert. Dr. Danforth mentioned eleven failures.

DR. JOSEPH B. DELEE, CHICAGO, ILL.—I would like to recommend to the Fellows the introduction of parasacral anesthesia. Dr. Danforth mentioned that only the older anesthetics could be used to relax the cervix, but we have found that parasacral anesthesia is very practical and relaxes the lower uterine segment sufficiently so that these maneuvers can be done.

DR. EDWARD A. SCHUMANN, PHILADELPHIA, PA.—Our own conclusions and findings agree very closely with Dr. Danforth's. Ever since Pomeroy instructed us in the use of manual rotation of the occiput, I have been a devoted follower of his technic and in the years which have elapsed since that development I have tried in various ways to overcome the difficulties which sometimes occur in the manual rotation of the occiput. The chief difficulty in my hands has been the tendency of the head to slip back after manual rotation, and the necessity of keeping a hand in place when sliding the blade of the forceps in order to maintain rotation. Eventually there developed a simple manual variation of the original technic which the entire obstetric staff of the Kensington Hospital for Women have been using now for a number of years with almost uniformly good success.

The procedure consists in ignoring the head entirely, allowing it to repose in the bottom of the hand, while the finger seeks the anterior shoulder. Then with the operator's arm below the level of the delivery table a slow circular motion is carried out. Finally the head lies in the right anterior diameter, the anterior shoulder being in the anterior oblique position from which it originated. By this plan we have been able to rotate the great majority of the posterior occiputs which have resisted spontaneous rotation. When it fails, as it occasionally will with a firmly impacted head, the occiput in the hollow of the sacrum, and when we feel after due observation of the pelvis that it is probably incorrect to permit the patient to deliver as an occiput posterior, which we consider a normal delivery in certain types of contraction and do permit to take place, we rely almost entirely upon the Kielland forceps.

DR. L. A. CALKINS, KANSAS CITY, MO.—Dr. Danforth emphasized the importance of the use of the assisting abdominal hand. We have been able in a very large number of cases to rotate the head by the use of the abdominal hand alone, plus the anesthesia of course.

DR. HUGO EHRENFEST, ST. LOUIS, MO.—Agreeing fully with everything said by Dr. Danforth, I would like to mention two details in my technic of manual correction. The occipitoposterior head as a rule is somewhat deflected, therefore when grasped for the purpose of rotation, pressure should be exerted on forehead to favor flexion. When this is accomplished, I give two or three minims of pituitrin, simply to push the head a little deeper into the pelvis, into its corrected position.

DR. FRED L. ADAIR, CHICAGO, ILL.—It is desirable to maintain nutrition during the first stage, but one should always keep in mind the probability of having to administer a complete anesthesia. In fact, we had one fatal case from aspiration pneumonia, and we feel that the patient should have a nonresidue diet during the first stage.

The greatest difficulty with occiput posterior positions is that they never complete the first stage, and I would like to have Dr. Danforth enlighten me as to how he handles those cases. With rupture of the membranes we often get fetal distress and later maternal exhaustion and are almost forced to resort to some interference.

DR. DANFORTH, EVANSTON, ILL. (closing).—I agree to the desirability of maintaining the body fluids if the labor lasts any length of time.

I am in agreement with Dr. Calkins' idea about the assisting hand. I have felt that the abdominal hand can be used with very marked benefit in helping to get the head around.

In reply to Dr. Adair the one fetal death should be reckoned in the number of posterior cases. In this report we are considering only term labors and not prematures.

I agree with Dr. Adair that the cases which do not attain complete dilatation are difficult to deal with. I prefer to obtain as much dilatation as is possible by the forces of labor, avoiding exhaustion of the woman, and, if unavoidable, to complete the dilatation manually. This is done only when it seems essential and as infrequently as possible.

Concerning the impacted head, if the head does not enter the pelvis we do not rotate. Engagement having occurred, we do not hesitate to displace the head upward and rotate, after which forceps are applied. As it has already entered the pelvis it will, as a rule, easily come in again.

Version was done when manual rotation was impossible or had failed. In one case the procedure advocated by Dr. Piper was used, about 600 c.c. of weak soap solution being injected into the uterus prior to version.

A method of rotation by the shoulder, as suggested by Dr. Schumann, is sometimes used if rotation of the head is difficult.

13. **Hernias Into the Broad Ligament and Remarks on Other Intra-abdominal Hernias.** Drs. James C. Masson and W. Atkinson, Rochester, Minn. (See page 731, November, 1934, issue.)

DISCUSSION

DR. C. J. MILLER, NEW ORLEANS, LA.—Hernia into the broad ligament is unquestionably the rarest type of hernia so far reported in the abdominal cavity. Only 13 authentic cases of strangulation from defects of the broad ligament are found in the literature, and only two cases were noted in which such defects were present and unassociated with strangulation. Hunt reviewed the cases, in a recent number of *Surgery, Gynecology and Obstetrics,* and states that in cases in which pouches were the offending defect, congenital anomalies may be strongly suspected. An interesting feature of the cases was that practically all of them were in women who had borne children. The older multiparae were almost exclusively affected, but nulliparous women were not immune.

The Baldy-Webster operation may be looked upon as an etiologic factor. I am able to report one case of hernia through the broad ligament, following a Baldy-Webster operation. Three years after a suspension operation had been done, the patient complained of constant pelvic discomfort, and was not relieved by rest or other measures. An exploratory operation was done, and an opening was found from the broad ligament alongside of the round ligament. Strangulation had not occurred. It was easy to close the opening and this procedure entirely relieved her.

DR. FLOYD E. KEENE, PHILADELPHIA, PA.—One example of herniation through the opening in the broad ligament has come under my observation. This patient was admitted to the hospital with the characteristic symptoms of an acute intestinal obstruction and at operation it was found that a loop of the terminal ileum had slipped through a congenital opening in the broad ligament, situated just beneath the round ligament at the junction of its outer and middle thirds. Release of the intestine was easily accomplished by dividing the round ligament.

DR. JOSEPH B. DELEE, CHICAGO, ILL.—This condition has been found more often in multiparous women and I think it may sometimes be due to a hematoma in the broad ligament which is not observed. Also the low cervical cesarean section may, I believe rarely, lead to hernia in the broad ligament. A hernia of the broad ligament was found at a second low cervical cesarean section. I did not force the forceps through the broad ligament at her first section, since a motion picture which was made of the operation shows it was correctly performed. One should not fail to lift up the edge of the cervical wound with an Allis forceps and slip the instrument under the wound edge to avoid this error.

DR. LILIAN K. P. FARRAR, NEW YORK CITY.—The fallopian tube is enclosed in a fold of peritoneum and the two edges of the peritoneum adhere to one another below the tube. I have found it very easy to separate these edges (and push in the fimbriated end) in doing a temporary sterilization of the tube. I think it is by such a separation of the peritoneum that a hernia in the broad ligament might occur.

DR. WILLARD R. COOKE, GALVESTON, TEXAS.—I have seen two colored women with congenital fenestration of the broad ligaments, but without hernia in either case. We had one hernia through the opening caused by a Baldy-Webster operation, with no particular features of interest.

DR. MASSON (closing).—This discussion illustrates the fact that the condition of hernia into or through the broad ligament is probably more common than the literature would lead us to believe. I think that if the condition is looked for by all gynecologists and abdominal surgeons it will be more frequently observed.

Dr. Miller mentioned his case following the Baldy-Webster operation. This impresses upon us the necessity, whenever that operation is performed, of following the advice of both Baldy and Webster of stitching the edge of the ligament firmly to the broad ligament.

I would look upon hysterectomy as a radical procedure in cases where there is strangulation. The indication in such cases is to complete the operation as soon as possible. The simplest operation would be to cut down to the edge of the opening, even if it were necessary to cut through the broad ligament, the round ligament and the fallopian tube, but I would be slow to add to the difficulty by doing a hysterectomy. If there were an opening on both sides, as recorded in some of the cases, especially those following the Baldy-Webster operation, and no indication for saving the uterus, one would probably be justified in performing a hysterectomy.

There is no doubt as Dr. DeLee suggests that in low cesarean section care should be taken not to injure the broad ligament, and if it is injured it should be resutured.

Replying to Dr. Farrar, I think there were two cases in which the hernia occurred below the round ligament.

15. **The Present-Day Trend in the Treatment of Fibroids of the Uterus.** Drs. Joseph L. Baer, Ralph A. Reis, and Edwin J. DeCosta, Chicago, Ill. (See page 842, December, 1934, issue.)

DISCUSSION

DR. RAYMOND E. WATKINS, PORTLAND, ORE. (by invitation).—In an analysis of 100 cases of fibroids we found degeneration occurring in 48 per cent, which is higher than that of the authors' 19.4 per cent. No instance of sarcoma, however, was found in our series. Hyperplasia of the endometrium, so frequently associated with fibroids, probably also acts as an etiologic factor. In our cases we found 44 per cent of hyperplasia of the endometrium and of these 23 per cent were polypoid in character. The tendency of polypoid endometrial growths to become malignant is well recognized.

Sterility in women having fibroids is still the subject of much discussion. Our authors believe that tubal disease is of more significance than the presence of the fibroid. As far as sterility is concerned, we wish to concur in this opinion. In cases we have studied there were 16 per cent with absolute sterility, including 4 per cent single women. If the latter were deducted, this would leave but 12 per cent. However, 17 per cent of our patients had repeated abortions, being unable to carry pregnancy to term. If those of absolute sterility were added to those who were unable to go on with pregnancy, it would mean that 29 per cent were unable to reproduce. The position of the tumor in the uterus seems not to be important, the abortions occurring in the subperitoneal type as often as in the submucous fibroid. Uterine irritability undoubtedly is the important factor here.

DR. FLOYD E. KEENE, PHILADELPHIA, PA.—I shall limit my remarks to but one phase of the subject, namely the incidence of menopausal symptoms after irradiation and after hysterectomy with and without ovarian conservation.

Recently we have reviewed the results obtained in 500 cases of myoma and the incidence of menopausal reactions following various methods of treatment is summarized in Table I.

TABLE I. SUMMARY OF MENOPAUSAL SYMPTOMS

| | RADIUM GROUP | ROENTGEN GROUP | HYSTERECTOMY WITH OVARIAN CONSERVATION | HYSTERECTOMY WITH BILATERAL OOPHORECTOMY | HYSTERECTOMY AND OVARIAN CONSERVATION WITH CONTINUED MENSTRUATION |
|---|---|---|---|---|---|
| None | 31.9% | 12.5% | 82.5% | 20.2% | 98.4% |
| Mild | 28.8% | 25.0% | 11.1% | 37.5% | 1.6% |
| Moderate | 22.6% | 37.5% | 2.5% | 17.3% | 0.0% |
| Severe | 16.5% | 25.0% | 3.9% | 25.0% | 0.0% |

Until a few years ago, our usual radium dosage was 1,200 mg. hours and a considerable proportion of our patients were in the late thirties and the early forties. Under these conditions, the incidence of severe menopausal reactions was over 30 per cent. More recently the dosage has been reduced to 600 mg. hours and the age limit extended to a minimum of 45 in most instances, and, as a consequence, the incidence of severe menopausal reactions has been cut in half, the effects on bleeding and tumor regression remaining about the same as with the larger dosage.

In the operative group, the value of ovarian conservation is clearly proved, since in four-fifths of the patients so treated no menopausal symptoms had developed, contrasted with one-fifth of those subjected to bilateral oophorectomy. Further the incidence of severe menopausal symptoms is six times greater in the latter group.

Approximately 20 per cent of our patients under forty-five years of age have continued to menstruate scantily after hysterectomy with conservation of one or both ovaries. In this group, more than 98 per cent have had no menopausal symptoms and in none did annoying reactions develop.

DR. BAER (closing).—The severity of the symptoms of the postradiation menopause is in direct relation to the prematurity of the induced menopause. Thirty-five years was the original arbitrary age limit under which radiation was contraindicated. General experience has raised this level to forty years. In this series 24.3 per cent of women were still menstruating at forty-six years of age. For this reason it seems desirable to consider radium, if at all, only in the fifth decade and as close to the expected menopause as can be determined.

It is further to be noted that radium is contraindicated after the menopause is established.

With regard to the failures with radium, Norris reports 8 per cent failures, Schmitz 12 per cent, Ford 21 per cent and Keene 6.5 per cent. In our series the total incidence of failures was 11.1 per cent.

Concerning ovarian conservation, the reasons for removal of one or both ovaries are not entirely dependent on the presence of pathology. There are two other reasons that have to be considered. One is mechanical. If the fibroids are so placed, conservation of the ovary becomes mechanically impossible, and it has to be sacrificed. Last, if the nutrition of an ovary is sufficiently disturbed by the removal of the fibroids, the ovary has to be removed as a prophylactic measure against cystic degeneration.

16. **The Nature of Ovary-Stimulating Hormones.** Dr. C. Frederic Fluhmann, San Francisco, Calif. (See page 668, November, 1934, issue.)

DISCUSSION

DR. EMIL NOVAK, BALTIMORE, MD.—With reference to the rôle of the anterior hypophysis, there are still two chief moot points. One is the relationship between the

anterior pituitary sex hormones themselves and the prolan found in the urine of pregnant women. There has been much interesting discussion, particularly in the German literature as in the long drawn out controversy between the two schools, championed on the one hand by Zondek, and on the other by Philipp. My own feeling has been that Philipp and his school have the better of this argument, and that the weight of evidence indicates that prolan is not the same as the anterior sex hormone itself, being probably of trophoblastic origin.

The other moot question is whether the follicle ripening hormone is separate and distinct from the luteinizing hormone or whether they simply represent different phases of activity of a single sex principle. Here the question is still a wide open one, with many excellent workers on both sides.

So far as the actual hormonic interchange or interplay in menstruation is concerned, the evidence is quite good on most points. I cannot criticize Dr. Fluhmann's theory because it is about the same as I have been teaching for a considerable time. There is much reason to believe, as Dr. Fluhmann has suggested, that the factor which keeps the corpus luteum active probably comes from the ovum, and that when the ovum has imbedded itself it is probably the chief source of those chemical messengers which, through the anterior pituitary, maintain the activity of the corpus luteum for such a long time after the onset of pregnancy.

DR. OTTO H. SCHWARZ, ST. LOUIS, MO.—So far as I know, no human ovum has been found in the uterus at autopsy or operation when there was a definite history of the individual not missing her menstrual period. Since ovulation and impregnation, in most instances, must take place between the sixteenth and twentieth day of the cycle, the transit of the impregnated human ovum through the tube is most likely similar to that in the guinea pig.

Both gross and microscopic specimens of the premenstrual endometrium on the twenty-eighth day of the cycle, show changes which would not be compatible with the implantation of the ovum. It would, therefore, seem logical to assume that continued development of the corpus luteum and the prevention of retrograde change in the premenstrual endometrium, result from some stimulating substance given off by the impregnated ovum while it is traveling through the tube still within the zona pellucida. The stimulation may primarily affect the corpus luteum or affect it secondarily through a primary stimulation of the anterior lobe of the pituitary gland.

DR. FRED L. ADAIR, CHICAGO, ILL.—There is essential danger in the use of the anterior pituitary hormone. We had a young girl under observation who had not menstruated. Her pelvic findings were essentially negative except possibly for a little hyperplasia of the uterus. An attempt was made to use this stimulating hormone and as a result the patient developed some rather large ovarian cysts which proved to be follicle cysts. The same preparation was subsequently tried on an older woman who was scheduled for operation, in order to see whether we could repeat this performance, and it was found that she also developed a rather large follicle cyst in the ovary. Therefore, I think we should be rather cautious in the use of this as well as other hormones in women and also that we should emphasize the evidence from those two observations that there may be some definite relationship between the formation of follicle cysts in the ovary and the gonad-stimulating hormone of the anterior pituitary.

DR. JOSEPH B. DELEE, CHICAGO, ILL.—I have noticed particularly since I have been using the colposcope, that women at the menopause and after supravaginal hysterectomy may develop polypoid conditions and real polypoid masses in the stump of the cervix, and I wonder if the cervix is not under hormonal influence, just as the endometrium is.

17. **Granulosa Cell Tumors of the Ovary.** Drs. Emil Novak and James N. Brawner, Baltimore, Md. (See page 637, November, 1934, issue.)

DISCUSSION

DR. BENJAMIN P. WATSON, NEW YORK CITY.—Dr. Novak's emphasis on the origin of these tumors from oophoronegenic rests is particularly important as giving an explanation of the diversity of their histologic character and in their symptomatology. It is extraordinary how long the old theory of the development of the ovarian follicles from an invagination of the so-called germinal epithelium has persisted. When we picture the true development of the ovary as a differentiation of one mass of cells into ova, follicle epithelium, and stroma, it is easy to imagine how such a group of those original cells, remaining as a rest, may develop into a tumor with epithelial-like cells, or into one with resemblances to a sarcoma; and how in all of them we may find histologic changes similar to those seen in the normal ovary during its various functional activities, and how these are capable of causing similar or exaggerated functional results.

In the past two years we have had two granulosa-cell tumors pass through the laboratory of the Sloane Hospital for Women; one patient was twenty-eight years of age, nulliparous, complaining of severe menorrhagia amounting to almost continuous bleeding, unaffected by various endocrine preparations. On examination a cyst the size of an orange was discovered in the right side of the pelvis. A curettage was done and the cyst, which replaced the right ovary, was removed together with the tube. The other ovary appeared healthy. The cyst measured 8.5 cm., was yellow to greenish-gray in appearance and contained clear amber fluid. In the wall, the inner surface of which was smooth, were smaller cystic spaces. Microscopic examination of the wall showed many of the appearances described by Dr. Novak, but chiefly the macro- and microfolliculoid types. In one area there was a definite lutein-like appearance. The endometrium showed a pronounced cystic glandular hyperplasia with little gland cell activity. Since operation this patient has had three normal menstrual periods.

The other case was discovered accidentally in the routine examination of specimens. Operation was undertaken for fibromyomas with associated adnexal inflammatory disease. The woman was colored, aged fifty-five, and had had the menopause five years before. Six months prior to admission she had had some vaginal bleeding, which lasted for only one day.

There was marked thickening and adhesions of the adnexa. The right ovary was enlarged to a size of 3.5 by 2 by 1 cm. Near one pole was a small circumscribed nodule. On microscopic examination this was found to be an epithelial tumor separated from the rest of the ovarian stroma by a definite connective tissue capsule and broken up into lobules by a connective tissue framework. The epithelial cells resemble granulosa cells. Some are in solid formation, and others are arranged in a folliculoid manner. The high power view shows the superficial resemblances to primitive follicles with central ovum to which Dr. Novak has referred. Tumor cells growing in solid formation are present in the connective tissue capsule and appear to be growing within endothelial lined spaces suggestive of lymphatics.

The endometrium in this case showed no hyperplasia. It had the atrophied appearance of the endometrium of a woman five years past the menopause.

As regards the procedure, when these tumors are diagnosed I am in entire agreement with Dr. Novak that in the younger woman we are justified in being conservative as regards the uterus and the other ovary, but that in the case of those near, at, or past the menopause, complete removal of the uterus and both adnexa is the method of choice.

DR. CAREY CULBERTSON, CHICAGO, ILL.—Dr. Novak included among the granulosa-cell tumors the other tumors which are derived from the same source in the ovary, the so-called folliculomas and lutein cell tumors. He referred to the luteinization of the granulosa-cell tumors, but he did not specifically say that he included the so-called theconas. I think this terminology, was very well made because it reduces in number the terms that are required and makes it simpler for the teacher. However, in that respect, I think there will be some continued difference of opinion on the part of the pathologists who will not yield to the idea that these tumors are all granulosa-cell tumors, merely changed because the hormone, or whatever substance it is that affects development of their cells from the undifferentiated residue of the mesenchymal nucleus, causes them to appear in these various forms. The pathologist will continue to regard the theca-cell tumor as different from the granulosa-cell tumor even if, as is true, they both affect similarly the uterine endometrium. The pathologist is apt to emphasize the differences rather than similarities. It is possible therefore to mistake the theco.na, and this tumor has been most often mistaken for sarcoma and often looks more like it than like a granulosa-cell tumor. With regard to malignancy, I am in accord with Dr. Novak's views. If these tumors take their origin in the undifferentiated residue we should expect to see the peculiarities characteristic of malignancy. But here again pathologists are none too helpful. Only recently no less an authority than McCarty has asked the question as to whether the cancer cell possesses any differentiating characteristics. Likewise research workers in embryology have suggested that growth and differentiation of early embryonic tissues are determined largely by intracellular "organizers" or chemical "energizers."

DR. FRANK W. LYNCH, SAN FRANCISCO, CALIFORNIA.—In seeking an etiology for these tumors, we are likely to revert to Waldeyer's and Pfluege's idea of the origin of the ova, theories that have been overthrown. Evans, in a publication which has not been as widely circulated as it deserves, has shown that the ova in human beings and in laboratory animals are not preformed at birth but are developed each month from germinal epithelium. So, instead of being the oldest cell in the body as we have been taught for years, we find that an ovum lasts only for a few days, probably as long as a red blood cell. Did the ova live as long as we have been led to believe they did and were always preformed at birth, inherited characteristics would be the only ones that we would be likely to develop.

These tumors are very interesting clinically in some women with unexplained hemorrhages and negative findings on examination. I have had two patients in recent years whom I had treated with radium even though I found no evident reason for the bleeding. When the bleeding returned again after several months' freedom, I removed the pelvic organs, after having carefully explored the entire abdomen. I found small granulosa cell tumors in each case: In one of them the ovary was of normal size. My entire staff now suspect the presence of this type of tumor when a woman is bleeding, and uterine cancer has been excluded by curetting, and an ovarian tumor has been ruled out by a negative pelvic examination.

The symptomatology of this tumor is very interesting. Usually, the patient with this neoplasm feels so well that she believes the bleeding is merely an indication of the return of youth. Rarely, however, the reverse holds. One of my patients with a rather large granulosa cell tumor was extremely depressed before the tumor was removed but was really rejuvenated afterward. The tumor in this case was large enough to be malignant, although the patient died a year later from an endocarditis before she had widespread metastases.

DR. NOVAK (closing).—I am familiar with the work of Evans and Swezy on the question of postnatal ova-genesis, which they think possible even in the human ovary.

While I have much respect for these investigations, I have not been convinced that their correctness has been demonstrated in the human being. While the possibility of germ cell formation even in adult life must be borne in mind, we have not seen any evidence of it as yet.

Referring to Dr. Culbertson's remarks about the thecal-cell tumors, I was impressed when the recent paper of Melnick and Kantner appeared, with the similarity of their cases with one or two of ours; moreover, the endometrial picture was exactly the same as in our granulosa-cell tumors. In many of our cases, we could see a transition from a sarcoma-like picture to the more typical epithelial picture. On the basis of the newer developments in ovarian embryology there seemed to be no justification for making a distinction between the two groups of tumors. We have, however, discussed this question more fully in the body of our paper.

Finally, it is interesting to remark, because I think it has a bearing upon the question of the etiology of vasomotor symptoms in menopausal women, that in our Case 20, the woman having already had one menopause at forty-seven, after removal of her tumor at fifty-seven went through a perfectly characteristic second menopause, with typical vasomotor symptoms. One of Schulze's patients showed the same phenomenon as did another case reported by Dworzak. This is interesting because it indicates that folliculin withdrawal is probably the initial cause of these menopausal symptoms, and makes our treatment of these with follicle hormone quite rational. At certain stages we normally get a drop in the level of follicle hormone, and it is in these cases that we get the most vasomotor symptoms. On the other hand, at certain other phases, as Zondek has shown, there is a hyperfolliculinism, and in these we are more apt to note menstrual excess. My observation has been that menopausal symptoms are usually absent or slight in menopausal women suffering with functional bleeding.

18. **The Influence of Pregnancy on Tumor Growth.** Dr. L. A. Emge, San Francisco, Calif. (By Invitation.) (See page 682, November, 1934, issue.)

DISCUSSION

DR. BROOKE M. ANSPACH, PHILADELPHIA, PA.—I always had been under the impression that cancer of the cervix increased with great rapidity during pregnancy. Dr. Emge's observations seem to show otherwise; five permanent cures out of six cases is very striking. This brings up the problem not only of the etiology of cancer but also of the cure of cancer. The similarity between the destructive action of a cancer cell and the destructive action of a chorion cell during nidation of the ovum is well known. Why does this destructive action cease physiologically at a certain time during placentation? Is the failure of the inhibiting influence the underlying cause of chorionepithelioma? What continues the normal into the pathologic and what is the significance of the unusual quantity of the anterior pituitary or the anterior pituitary-like hormones that appear in the blood with the development of a chorionepithelioma? These unexplained facts certainly open up many interesting fields of conjecture.

DR. J. C. LITZENBERG, MINNEAPOLIS, MINN.—It is sometimes a thankless job to tear the curtain from popular fallacies as Dr. Emge has done. His experiments have shown just about what we might expect. Clinically, observations may have led us astray, and yet they have been quite justified in the limited light of existing knowledge. When we see a uterus in a patient less than three months pregnant, with a tremendous myoma, we might be excused for concluding that the myoma grew unusually rapid, and yet Dr. Emge's experiments have shown that this tumor growth

is *pari passu* with the uterus, due undoubtedly to the fact that myomas being constructed of the same tissue as the uterus, respond to the same hormonal stimulation.

Dr. Emge confirmed in his experimental work the fact that ovarian tissue tumors do not usually grow. These are usually small cysts but even good-sized ones may be hidden behind the uterus and discovered only after delivery.

His experiments show, as clinical experience would anticipate, that only those tumors increase which are capable of hormonal stimulation.

DR. EMGE (closing).—In regard to cancer of the cervix in pregnancy, I still believe that the degree of curability is largely dependent upon whether or not this tumor is discovered early. The mere fact that fibroids are more readily discernible during pregnancy does not necessarily indicate that they grow. It was demonstrated by Borner that many of these tumors migrate toward the surface during the progressive enlargement of the uterus, which makes them more readily available to the tactile sense. The enlargement of pure leimyomas may be considered an actual growth response, since involution is less marked than in fibromyomas or fibromas. I have studied some 40 fibromyomas removed during pregnancy and have invariably found that active cellular hypertrophy comes to a standstill somewhere near the sixth month. In most of these tumors the apparent enlargement of cells, particularly muscle cells, could be easily explained on the basis of a marked increase in intracellular fluids. In only a few of these tumors could we demonstrate sufficient hypertrophy to allow us to believe that the tumor had actually grown. We have not been able to demonstrate to our satisfaction that hyperplasia is an important factor in the enlargement of fibroids during pregnancy.

19. **Demonstration of the Lymphatic Circulation in the Pelvis of the Living Woman by the Roentgen Rays.** Dr. George Gellhorn, St. Louis, Mo. (See page 769, November, 1934, issue.)

20. **The Innocuousness of Rupture of the Membranes Early in Normal Labor.** Dr. Edward L. King, New Orleans, La. (See page 763, November, 1934, issue.)

DISCUSSION

DR. JOSEPH B. DeLEE, CHICAGO, ILL.—I believe that the principle that the bag of waters is a protective mechanism for the cervix still holds. If one knows the physics of the uterine action he will easily see the dilating effect of the bag of waters on the cervix; if one denies the bag will dilate the cervix, he must admit the head also will not do so after the membranes are ruptured. Rupture of the membranes is dangerous. In transverse presentation the dilatation is almost completed without the bag of waters but it is not the complete dilatation as you get it with the normal mechanism. Now when the cervix dilates the longitudinal fibers pull up all the tissue, but the mucous membrane may follow too slowly and if the membranes are ruptured the endocervical mucosa is forced down by the head like a glacier slide and produces a condition like an everted anus. Injury of the cervix is one of the causes of the numerous cervical infections.

As to the baby's brain, there are silent areas in the brain which do not reveal their injuries when the baby is young. When the bag of waters is intact the baby's brain is protected and after it is ruptured the brain gets the full force of the action of the uterus. That has been proved in a rather crude way by experiments on guinea pigs, in which the brain was trephined with resulting increased blood pressure, hyperemia, etc.

DR. H. J. STANDER, NEW YORK CITY.—From our experiences at the Lying-In Hospital I agree with the conclusions of Dr. King. It seems fairly well established

that the bag of waters does not play as important a rôle in the dilatation of the cervix as we have heretofore believed. The work of Guttmacher and Douglas, as well as that of Quigley, showed fairly conclusively that labor is not lengthened by early rupture of the membranes.

I have reviewed 4,250 consecutive full-term and premature deliveries. Of this group 2,047, or 48 per cent, had ruptured membranes, either spontaneously or artificially, prior to the second stage, which means either before labor started or during the first stage of labor. In Table I is shown the time of rupture of the membrane in these 2,047 patients. In only two cases did we induce labor by rupture of the membranes; and in only 7.06 per cent of the cases were the membranes ruptured artificially, for some reason or other, prior to the second stage.

Table II shows that in 92 per cent or more of these cases, the presentation was vertex. The incidence of puerperal infection, as shown in Table III, is about 10 per cent in the patients in whom the membranes ruptured spontaneously prior to the

TABLE I. TABLE SHOWING TIME OF RUPTURE OF MEMBRANES

| | PREMATURE DELIVERY | FULL-TERM DELIVERY | | TOTAL | % OF 2,047 |
|---|---|---|---|---|---|
| | | OPERATIVE | SPONTANEOUS | | |
| Labor induced by rupture of membranes, artificially | 0 | 1 | 1 | 2 | 0.097 |
| Membranes ruptured spontaneously before onset of labor | 34 | 183 | 522 | 739 | 36.10 |
| Membranes ruptured in 1st stage of labor | 33 | 323 | 950 | 1306 | 63.80 |
| Spontaneously | 24 | 254 | 872 | 1150 | 56.2 |
| Artificially | 9 | 69 | 78 | 156 | 7.6 |

TABLE II. NUMBER OF CASES WITH VERTEX PRESENTATION

| | PREMATURE DELIVERY | FULL-TERM DELIVERY | | TOTAL | GRAND TOTAL | % GRAND TOTAL |
|---|---|---|---|---|---|---|
| | | OPERATIVE | SPONTANEOUS | | | |
| Labor induced by artificial rupture of membranes | | 1 | 1 | 2 | 2 | 100 |
| Membranes ruptured spontaneously before onset of labor | 28 | 144 | 510 | 682 | 739 | 92.28 |
| Membranes ruptured in 1st stage of labor | 24 | 256 | 931 | 1211 | 1306 | 92.72 |
| Spontaneously | 18 | 192 | 855 | 1065 | 1150 | 92.60 |
| Artificially | 6 | 64 | 76 | 146 | 156 | 93.58 |

TABLE III. NUMBER OF CASES OF PUERPERAL INFECTION*

| | PREMATURE DELIVERY | FULL-TERM DELIVERY | | TOTAL | GRAND TOTAL | % GRAND TOTAL |
|---|---|---|---|---|---|---|
| | | OPERATIVE | SPONTANEOUS | | | |
| Labor induced by artificial rupture of membranes | | 0 | 0 | 0 | 2 | 0 |
| Membranes ruptured spontaneously before onset of labor | 5 | 35 | 31 | 71 | 739 | 9.60 |
| Membranes ruptured in 1st stage of labor | 2 | 71 | 74 | 147 | 1306 | 11.25 |
| Spontaneously | 1 | 57 | 61 | 119 | 1150 | 10.34 |
| Artificially | 1 | 14 | 13 | 28 | 156 | 17.94 |

*In 2,620 full-term + premature deliveries in 1933 there were 228 cases of puerperal infection. *Incidence* = 8.702 per cent.

onset of labor, as well as in those cases in whom the membranes were ruptured in the first stage of labor. This is approximately the incidence of puerperal infection for the whole clinic, the figure being 8.7 per cent. When, however, we consider the patients in whom the membranes were ruptured artificially, the incidence of puerperal infection is definitely elevated, being 17.9 per cent. In 26.9 per cent of these patients labor was definitely prolonged to thirty hours or more. This undoubtedly is one factor in the increased incidence of infection. Although in the present study all other factors have not been evaluated, and we are unable to definitely ascribe the higher morbidity to the artifical rupture of the membranes, we feel that this increased incidence of puerperal infection in the patients with artificially ruptured membranes must be taken as a note of warning and that the rupture of the membranes, as a means of inducing labor, must not be regarded too lightly with respect to infection.

Table IV shows the incidence of infantile mortality, in the various groups of patients in whom labor was induced artificially, by rupture of the membranes, as

TABLE IV. INFANTILE MORTALITY*

| | PREMATURE DELIVERY | FULL-TERM DELIVERY | | TOTAL | GRAND TOTAL | % GRAND TOTAL |
|---|---|---|---|---|---|---|
| | | OPERATIVE | SPONTANEOUS | | | |
| Labor induced by artificial rupture of membranes | | 0 | 0 | 0 | 2 | 0 |
| Membranes ruptured spontaneously before onset of labor | 10 | 18 | 11 | 39 | 739 | 5.27 |
| Membranes ruptured in 1st stage of labor | 12 | 40 | 16 | 68 | 1306 | 5.21 |
| Spontaneously | 6 | 27 | 13 | 46 | 1150 | 3.10 |
| Artificially | 6 | 13 | 3 | 22 | 156 | 14.10 |

*In 2,651 full-term + premature infants in 1933 there were 121 infantile deaths. *Incidence* = 4.565 per cent.

well as in those in whom the membranes ruptured, either spontaneously or artificially, during the first stage. Here again it will be noted that there is a marked difference between the patients with spontaneous rupture of the membranes and those with artificially ruptured membranes. The fetal mortality in the later group is 14.1 per cent, as compared with the clinic incidence of 4.5 per cent.

From this short study I am led to believe with Dr. King that the less we interfere with the normal progress of labor, so long as it is normal, the better will be our results. We do not hesitate to employ rupture of the membranes for the induction of labor where we feel that it is indicated, but we are convinced that it is not the procedure of choice in all patients where labor should be initiated.

Two factors are of extreme importance in determining the latent period and the success of this method of induction of labor; these are the length and the dilatation of the cervix. The latent period, as Guttmacher and Douglas showed, is lengthened nearly four times in patients with long cervices, compared to those with shorter cervices. The length of the cervix could also be directly correlated to the duration of the labor, the longer the cervix the longer the labor. Furthermore, dilatation of the cervix affects the latent period, patients with closed cervices having a long latent period, and patients with patent cervices having shorter latent periods. However, the dilatation of the cervix at the time of the rupture of the membrane does not materially affect the duration of labor.

From this we must conclude that rupture of the membranes, before labor or early in labor, either artificially or spontaneously, in a patient with a long, closed cervix carries with it two possibilities, a long latent period and a long labor, both of which must necessarily be associated with increased complications to mother and child. It

must, therefore, be clear to all that rupture of the membranes as a means of induction must be carried out in carefully selected and studied patients, and is not a method that can be applied to all patients without serious consequences.

DR. WILLIAM E. CALDWELL, NEW YORK CITY.—The x-rays have shown that the normal position of the babies is transverse and the function of the rotation is not only to straighten the child's body but to bring it forward toward the front of the uterus. The early rupture of the membranes apparently allows this process to be established much more quickly than if the membranes are intact. We all feel safe, as far as the baby is concerned, when the membranes are intact.

DR. JOSEPH L. BAER, CHICAGO, ILL.—I have the definite feeling that if Dr. King wants an endorsement from the American Gynecological Society of the relative safety of artificial rupture of the membranes in ordinary uncomplicated labor, that endorsement should be withheld. I cannot help but feel that the innocuousness of artificial rather than spontaneous rupture depends on the character of the cervix and the entire labor picture; in other words, it is a situation which demands clinical judgment. We all rupture the membranes under certain conditions, but to proclaim it as a legitimate procedure merely with the thought that it will expedite labor, will lead the profession at large into many unhappy predicaments.

DR. KING (closing).—I do not wish to be misunderstood as advocating the indiscriminate rupture of membranes early in labor merely for the purpose of expediting labor, nor do I feel that the rupture is at all times innocuous nor that the protection to the fetal head can by any means be disregarded. Fitzgibbon said that he is fully convinced that the bag of waters does not play any part in the dilatation of the cervix. That, I think, is not correct and desire to emphasize my conclusions.

I do not want to leave the impression that an early case of rupture of the membranes is entirely innocuous, but that in early cases we should hunt for dystocia or difficulties that may be encountered and be prepared for them. If we cannot find abnormalities we can feel reasonably comfortable and should not be forced or hastened into unwise and unnecessary procedures. The induction of labor by artificial rupture of the membranes is still in the experimental stage. It seems to have brought good results but I think we must watch very carefully the use of pituitrin in combination with this procedure.

21. **Total Abdominal Hysterectomy: Anatomy and Technic.** Dr. Lillian K. P. Farrar, New York City. (Original paper appears in the current volume of the Society's Transactions.)

22. **A Report of 565 Vaginal Hysterectomies Performed for Benign Pelvic Disease.** Dr. N. Sproat Heaney, Chicago, Ill. (See page 751, November, 1934, issue.)

DISCUSSION

DR. HAROLD O. JONES, CHICAGO, ILL.—We believe that the average mortality and morbidity in complete hysterectomy is considerably higher than that given in this report today. Figures thus obtained are not from parallel cases. The mortality figures are not so much influenced by the removal of the cervix, but by the natural increased risk from time-consuming traumatic dissection of adnexal pathology.

In an unreported series of 100 cases operated by a member of this Society where the pathologic conditions were exactly parallel, the mortality and morbidity in complete removal was more than two times that in the supracervical operation.

In our clinic we have never been able to demonstrate that any infection has come from a supravaginal amputation of the cervix. We are further convinced that evi-

dence has not yet been produced to necessitate the removal of the cervix after removal of the uterus on account of any increased incidence of carcinoma of the cervix. It has not yet been established that cervical lacerations and infections are definitely connected as an etiologic factor in carcinoma. We believe that the discharges and various conditions of the cervix can be controlled much more simply by subsequent cautery.

With regard to Dr. Heaney's paper, we very strongly subscribe to the vaginal method of removing pelvic tumors, but have restricted our procedures to those that are easily accessible, freely movable, and those that are present in women who have some relaxation. We have not yet had the temerity to attack the larger tumors in nulliparous women. In women with considerable relaxation we prefer the vaginal route.

Our technic differs somewhat from that illustrated in Dr. Heaney's picture in that we dissect considerably more in trying to correct the relaxations. Two years ago we reported 2,500 plastic operations, including 168 complete vaginal hysterectomies, done over a period of ten years and in those ten years we had a mortality of three, which again emphasizes the point that Dr. Heaney made of the marked reduction in mortality and morbidity in cases operated upon by the vaginal route.

DR. EDWARD H. RICHARDSON, BALTIMORE, MD.—Dr. Farrar has built up a strong argument, to be sure, in favor of complete as compared with subtotal hysterectomy. Nevertheless and in spite of the fact that I too sponsor an operative technic for complete hysterectomy, I cannot help but feel that, except in the larger clinics and in the hands of experienced gynecologists, there will undoubtedly be both a higher mortality and a greater morbidity following the complete operation than would be the case in the incomplete one. I think this is also true with reference to vaginal hysterectomy in the more difficult types of cases. I do not routinely remove the cervix. I do so only when I can be satisfied that there is some demonstrable pathology that will predispose to the development of carcinoma, or where there are cystic glands with the possibility of focal infection. I think in that group of cases the cervix should be removed, but where there is a perfectly normal cervix I cannot yet bring myself to believe that the operative procedure is as simple and as safe as subtotal hysterectomy.

I am not yet prepared to report on a sufficient number of my own panhysterectomies. I have not yet reached my first one hundred cases but have had no mortality and no serious morbidity.

I am sure all of us are impressed with this series of cases of Dr. Heaney's in which he has had almost no mortality. Therefore, one may now safely choose between complete hysterectomy by the vaginal route or by the abdominal route and have available any one of a half dozen or more procedures from which he may suit his individual taste.

DR. GEORGE GRAY WARD, NEW YORK CITY.—I believe that there is great danger in cutting across the cervix. I will illustrate this by reciting one case I had some years ago at the Postgraduate Hospital. The patient had a fibroma. The routine supravaginal hysterectomy was done and the patient died within thirty-six hours of a virulent streptococcic infection. We were fortunate in getting an autopsy and as we got a pure streptococcus from the abdominal cavity, the uterus, which had not been disturbed, was opened and a pure streptococcus was obtained from the endometrium. Infection is often present there, and I cannot see how there would not be some danger in cutting across the cervix. In our service at the Women's Hospital in some 650 cases of cancer of the cervix we ran across 47 that had been subjected to a supravaginal hysterectomy, or 7 per cent. If those cases had had the cervix removed at operation, they would not have developed cancer of the cervix subsequently.

Another point is that I believe when it is necessary to irradiate a stump left after hysterectomy that we have a very definitely increased danger of injury to the bladder. With this conviction, having studied our complications quite carefully, when it is necessary to treat the stump I have reduced the initial dosage and repeat as necessary for fear of having an untoward result, by causing a fistula or even an intestinal injury. We had one case that came to autopsy with intestinal fistula and which showed the loop of intestine adherent to the cervical stump which had been irradiated. Therefore, given a case where we can without danger to the patient remove the whole uterus, it seems to me the wise thing to do. I, of course, recognize the point just made that there may be complications such as Dr. Jones spoke of. Very often the danger is materially increased in attempting to do a panhysterectomy. Where the cervix is normal, and the conditions difficult, my judgment would be to do a supravaginal hysterectomy, but where panhysterectomy can be done safely it is the desirable procedure.

DR. GEORGE GELLHORN, ST. LOUIS, MO.—What commonly goes under the name of abdominal hysterectomy is a misnomer. Hysterectomy means extirpation of the entire uterus, but what is being done in most instances, is only an amputation of the uterus. It is a sad reflection that many men who attempt pelvic operations are not sufficiently familiar with the technic of hysterectomy. The result is that all patients are subjected to one and the same type of operation, even if the condition of the cervix or other specific features of the case obviously call for a total removal of the uterus. I have in mind at this moment the case of a young woman of twenty-three who underwent a supravaginal amputation; the surgeon then put her in lithotomy position and sewed up a deep tear in the cervix. A year later she came into our clinic with a carcinoma of the cervix. That brings me to the problem of stump carcinoma. Dr. Farrar had 47 cases in her series. Only last month I reported 44 stump cancers. I maintain that we have at present no method of prevention of uterine cancer that is absolutely certain except the *total* removal of the uterus in all cases where we have to perform hysterectomy. That is the only known method of prevention of cancer; and it is the strongest argument in the controversy of total *versus* subtotal hysterectomy.

DR. WILLIAM P. HEALY, NEW YORK CITY.—I believe that we must not be too much influenced by what has been said about stump cancer since we must know in each case how early the symptomatology of the cancer appeared following the supracervical hysterectomy because the patient may have had cancer at the time of her hysterectomy. Although it is difficult to get correct figures on stump cancer following hysterectomies, we are unable to determine that more than four-tenths of 1 per cent are apt to develop cancer subsequently in the cervix.

Recently Dr. A. N. Arneson reviewed 2,600 cases of cervical cancer at the Memorial Hospital. There were but 67 cases in that series that could be regarded as legitimate cases of cancer developing in the cervical stump after a preceding supravaginal hysterectomy. He took as an arbitrary line of division the fact that the symptoms must not have appeared sooner than three years following the hysterectomy. I think that decision is reasonable because we know that cancer may remain latent in the cervix for a period of time before it becomes recognized. Taking that as his line of starting, only 67 out of 2,600 cases could be found or 2.6 per cent.

DR. FARRAR (closing).—The criticism has been made that total hysterectomy is time-consuming. When one is doing total hysterectomy routinely, it requires only a few minutes more to remove the cervix.

Dr. Ward spoke of infection in supravaginal hysterectomy. A culture made from the cavity of the uterus removed because of submucous fibroids or cancer in the fundus shows not infrequently a positive growth.

Irradiation for cancer of the cervix seems to have reached its peak. We know that despite heavy doses of radium that cancer often recurs, not only by metastases, but locally in the pelvis, and that high voltage x-ray of the pelvis does not destroy the carcinomatous glands and by stimulating connective tissue it does constrict the ureters. Renal insufficiency and death may follow from this compression.

It is of statistical interest only to know whether cancer in the cervix was recognized before or after a given date following a supravaginal hysterectomy. We know that prophylaxis is the best hope we have to lessen cancer and if a total hysterectomy be performed then an unrecognized cancer in the cervix would not be left nor could the patient develop cervical cancer later.

DR. HEANEY (closing).—I want to draw your attention again to the fact that in this series of cases there were four unsuspected carcinomas of the cervix, four carcinomas of the corpus uteri and three carcinomas of cervical polyps. When you do not suspect a carcinoma in a case you are operating upon vaginally and the whole operation is concluded without suspecting that a carcinoma is present, you may be sure that carcinomas will be overlooked much more often by the abdominal route, and particularly if operating supravaginally. There has never been any proof which I thought sufficient that lacerations of the cervix are productive of cancer of the cervix, and though removing the obviously diseased cervix will make the patient much more comfortable by relieving her of leucorrhea, yet if you leave the apparently normal cervix there is no evidence that you will lessen carcinoma of the stump subsequently.

Since I limited this paper to those cases which were benign and did not include the cases that were cancerous, I might say that there were 18 cancers of the body of the uterus without a death, and 25 cases of cancer of the cervix with two deaths. These cases were treated with an entirely different technic and hence were not included in this report.

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# Item

## American Board of Obstetrics and Gynecology

The next written examination and review of case histories of Group B applicants for certification will be held in various cities of the United States and Canada on Saturday, March 24, 1935. Case histories for review may be filed with the Secretary any time prior to this date after the approval of a candidate's credentials.

The general examination for all candidates will be held in the Atlantic City General Hospital on Monday, June 10 and Tuesday, June 11, 1935, immediately prior to the scientific session of the American Medical Association.

An unusual number of candidates is expected for this meeting, and on this account early application is advisable in order to qualify. Applications for Group B candidates must be received not later than February 23, 1935, and for Group A candidates not later than May 10, 1935.

For further information, booklets, and application blanks apply to the Secretary, Dr. Paul Titus, 1015 Highland Building, Pittsburgh, (6) Pa.

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## Errata

In the Caldwell article in the December issue of the Journal, page 838, Fig. 11 should be Fig. 9 and Fig. 9 should be Fig. 11.

In the same article on page 836 the following credit should appear under Fig. 8: From William's *Obstetrics* published by D. Appleton-Century Company.

# Books Received

THE STORY OF CHILDBIRTH. By Dr. Palmer Findley. With many illustrations. Doubleday, Doran and Co., Inc., Garden City, 1933.

THE STORK JOINS THE BLUE EAGLE. By Fred'k M. Margaretten, M.D. Illustrations by George S. Jacobs. Wamba Printery, Brooklyn, 1934.

AIDS TO OBSTETRICS. By Leslie Williams, Obstetric Surgeon to Out-patients, St. Mary Hospital, etc., London, tenth edition, William Wood & Co., Baltimore, 1934.

HEALTHY BABIES AND HAPPY BABIES. By Josephine Hemenway Kenyon, M.D. Little, Brown, and Company, Boston, 1934.

THE PROSPECTIVE MOTHER. A Handbook for Women During Pregnancy. By J. Morris Slemons, M.D. Third edition, D. Appleton-Century Co., Inc., New York, 1934.

OPUSCULA SELECTA NEERLANDICORUM DE ARTE MEDICA. Varii auctores de symphysiotomia. Aangeboden door het Nederlandsch Tjidschrift voor Geneeskunde, 1934.

MATERNAL MORTALITY IN PHILADELPHIA, 1931 to 1933. Report of committee on maternal welfare, Philip F. Williams, M.D., chairman, Philadelphia County Medical Society, 1934.

THERAPIE DER FRAUENKRANKHEITEN. Von Professor Dr. W. Benthin, Koenigsberg i.P. Mit 23 Abbildungen im Texte. Verlag von Urban & Schwarzenberg, Berlin and Wien, 1934.

HORMONE UND SEKRETION. Von Dr. Fritz Laquer, Professor an der Universitaet Frankfurt. Zweite, verbesserte und bedeutend erweiterte Auflage. Verlag von Theodor Steinkopff, Dresden, 1934.

THE CHEMISTRY OF THE HORMONES. By Benjamin Harrow, Ph.D., Associate Professor of Chemistry, City College of New York, and Carl P. Sherwin, M.D., of St. Vincent's and French Hospital. Williams and Wilkins Company, Baltimore, 1934.

DYNAMINCS OF POPULATION. By Frank Lorimer and Frederick Asborn. The Macmillan Company, New York, 1934.

TUMORS OF THE FEMALE PELVIC ORGANS. By Joe Vincent Meigs, Instructor in Surgery, Harvard Medical School, etc. With 261 illustrations. The Macmillan Company, New York, 1934.

SYNOPSIS OF PEDIATRICS. By Dr. John Zahorsky, Professor of Pediatrics, St. Louis University Medical School, etc. With 77 illustrations in the text and 6 color plates. The C. V. Mosby Co., St. Louis, 1934.

SYNOPSIS OF GENITOURINARY DISEASES. By Austin I. Dodson, Professor of Genitourinary Surgery, Medical College of Virginia, etc. With 111 illustrations. The C. V. Mosby Co., St. Louis, 1934.

STOEKEL'S HANDBUCH DER GYNAEKOLOGIE. Sechster Band, zweite Haelfte: Die Klinik der Uterus Tumoren bearbeitet von Esch, Martius, Pankow, Peham und Schoenholz. Mit 160 zum Teil farbigen Abbildungen im Text. Verlag von J. F. Bergmann, Muenchen, 1934.

CONCEPTION PERIOD OF WOMEN. By Dr. Kyusaku Ogino. Medical Arts Publishing Co., Harrisburg, Pa.

# Correspondence

## Pupillary Reactions in the Friedman Test*

*To the Editor:*

IN THE February, 1934, issue of this JOURNAL, Davis, Konikov and Walker describe a new method for reading the Friedman modification of the Aschheim-Zondek test. They observed the immediate eye reaction of the test animal following intravenous injection of urine. The criterion for a positive diagnosis was contraction of the pupils. Later, they also included dilatation of the pupils as an index of a positive reaction. They reported 87 per cent correct diagnoses in 154 positive tests and 80 per cent correct diagnoses in 97 negative tests.

In view of the simplicity of the method, we have attempted to confirm their findings. We have applied this method of reading to 100 clinical and 23 experimental tests. Our routine technic includes two intravenous injections of 7.5 c.c. of urine at twenty-four hour intervals with laparotomy forty-eight hours after the primary injection. Observations were made on 100 consecutive primary injections and 66 secondary injections. The experimental tests were made with fractional amounts of urine varying from ½ c.c. to $\frac{1}{80}$ c.c.

The data obtained in reading the pupillary reactions are presented herewith:

| | | |
|---|---|---|
| 100 primary injections | 7.5 c.c. urine | 50.0% correct |
| 66 secondary injections | 7.5 c.c. urine | 42.1% correct |
| 23 fractional injections | ½ c.c.–$\frac{1}{80}$ c.c. | 69.0% correct |
| 189 injections | | 53.4% correct |

Of 66 cases having two injections:

| | |
|---|---|
| Readings agreed after primary and secondary injections | 44 |
| Readings disagreed after primary and secondary injections | 22 |

Of 100 clinical tests: Friedman—pos. 52; Neg. 45; quest. 3
Eye react. pos. 60; neg. 40.

All eye readings were made under uniform lighting conditions. Of the 117 positive diagnoses made by observations on the eyes, contraction of the pupils were noted in all but 5, these latter showed dilatation. Each reading was checked by two observers.

Several interesting facts were noted. Most of the test animals, on being transferred from the cages to the injecting table showed definite dilatation of the pupils. As the animals rested, the pupils contracted. If the animal became at all excited, there was a very definite dilatation of the pupils, hence, if the rabbit jumped during the injection, it was most difficult to make a true reading of the pupils. Naturally, it was much easier to observe the pupils in white rabbits than in the darker strains.

Following the method of reading the Friedman test by observing the immediate effect on the pupil as outlined by Davis, Konikov, and Walker, we obtained correct readings in 53.4 per cent of 189 observations.

I do not believe that this method offers a reliable means of reading the Friedman test.

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